



NAVAL POSTGRADUATE SCHOOL

MONTEREY, CALIFORNIA

THESIS

**SURVIVING THE “STORM”: EXPANDING PUBLIC
HEALTH’S CAPABILITIES IN RESPONSE TO THE
INCREASING THREATS POSED BY NOVEL VIRUSES**

by

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December 2013

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HEALTH’S CAPABILITIES IN RESPONSE TO THE
INCREASING THREATS POSED BY NOVEL VIRUSES**

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ABSTRACT

As the planet's population continues to grow at rate that will see a global population of nine billion people by the year 2050, is an era being entered into which pandemics involving novel viruses are the new norm? If that idea is possible, then are drug therapies (approved by the FDA or in the pipeline for its approval) available that either limit virus replication within a host cell, or reduce the body's hyper-immune response (also known as "cytokine storm") to novel or pandemic strain viruses with which states could supplement their existing stockpiles?

This research explores six classes of medications that could potentially assist state-level governments in expanding their state-level stockpiles, to include more treatment and prophylaxis options, in the face of pandemics involving novel viruses. The results of this research were filtered through three criteria (medical efficacy, cost, logistical considerations) that narrow the field of candidate therapies down to four specific findings: one generic version of the antiviral called Ribavirin, and generic versions of the statins called Lipitor, Zocor and Gemfibrozil. This research may be applied to state and local-level public health agencies interested in bolstering their existing stockpiles for pandemic preparedness.

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LIST OF ACRONYMS AND ABBREVIATIONS

α	Alpha
a.k.a.	Also Known As
AIDS	Acquired Immunodeficiency Syndrome
ARDS	Acute Respiratory Distress Syndrome
B	Billion
BARDA	Biomedical Advanced Research and Development Authority
CDC	Centers for Disease Control and Prevention
CFR	Case Fatality Rate
CHDS	Center for Homeland Defense and Security
COPD	Chronic Obstructive Pulmonary Disease
CoV	Coronavirus
DHS	Department of Homeland Security
DHHS	Department of Health and Human Services
DPBH	Nevada Division of Public and Behavioral Health
DSNS	Division of Strategic National Stockpile
e.g.	Example Given
FDA	Food and Drug Administration
GAR	Gross Attack Rate
H (also referred to as HA)	Hemagglutinin
HCoV	Human Coronavirus
HIV	Human Immunodeficiency Virus
HPP	Hospital Preparedness Program
IV	Intravenous
JAMA	Journal of the American Medical Association
K	Thousand
M	Million
MCM	Medical Countermeasures
MERS-CoV	Middle Eastern Respiratory Syndrome-Coronavirus
mg	Milligram
MI	Managed Inventory

N (also referred to as NA)	Neuraminidase
N/A	Not Applicable
NIH	National Institutes of Health
NPI	Non-Pharmaceutical Intervention
NPS	Naval Postgraduate School
NPS/CHDS	Naval Postgraduate School, Center for Homeland Defense and Security
PAHPA	Pandemic and All Hazards Preparedness Act
PCV	Peace Corps Volunteer
PEP	Post-Exposure Prophylaxis
PHEP	Public Health Emergency Preparedness
PHP	Public Health Preparedness
PPE	Personal Protective Equipment
RNA	Ribonucleic Acid
Rx	Prescription
SARS	Severe Acute Respiratory Syndrome
SNS	Strategic National Stockpile
TCL	Target Capabilities List
VMAIQHS	Vaccination, Medication, Antivirals, Isolation, Quarantine, Hygiene, Social Distancing
WHO	World Health Organization

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In 1997, after completing a successful active-duty career with the U.S. Army, I made the unlikely choice of joining the U.S. Peace Corps to serve in the central African country of Gabon. It was during this two and a half year odyssey that I began what ended up being a new career in public health. I was assigned to one of the most influential people in my professional life, Madame Elizabeth Dindzona-Okaba, midwife to the Mimongo Child/Maternal Health Clinic. Everything I have achieved within public health derives directly from the lessons and advice she provided me. I have never forgotten what I witnessed and learned while serving in Mimongo, and the family and friends I met over there. I think of you all more often than you probably know.

Finally, I would be remiss if I did not reserve the highest praise to my beloved parents, John and Diane Mackie, who recently celebrated their 50th wedding anniversary together. You two have set a high standard as both parents and friends.

I. INTRODUCTION

Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible, is fever.

—Sir William Osler, *Science and Immorality*

A. PROBLEM SPACE

Within the Homeland Security enterprise there is perhaps no greater a threat posed, to both the health and welfare of Americans, as well as to the health and welfare of the globe's human population, than that of a global pandemic involving a novel virus. For all the progress humans have made on this planet, the age-old enemy of new viruses and the epidemics they ignite have been a persistent challenge throughout history. Humanity's collective memory is marked with great plagues, such as the "Black Death," and with imagery of such things as the "Fourth Horseman of the Apocalypse: Pestilence" that are incorporated into most holy scriptures.¹ With old enemies resurging, and new enemies emerging, is a new phase of the human experience beginning to occur globally, is an epidemic of epidemics being witnessed?²

That question, and the discussions it generated, has gained more momentum lately as humanity witnesses the emergence of separate, and concurrent, outbreaks of two new viruses: the H7N9 type-A influenza emanating from southeast China, and the Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) emanating from northeast Saudi Arabia.³ Within months of each other, two unrelated and "highly pathogenic" viruses (e.g., type-A influenza and a human coronavirus [HCoV]) have evolved to a point at which they each have successfully made 'the biological jump' from their animal

¹ Holy Bible (English Standard Version). Biblia.com, "Revelation 6:7–8, n.d., <http://biblia.com/bible/esv/Re6.7-8>.

² Arno Karlen, *Man and Microbes: Disease and Plagues in History and Modern Times* (New York, NY: Simon and Schuster Paperbacks, 1996), 11.

³ World Health Organization [WHO], "Global Overview of an Emerging Novel Coronavirus (MERS-CoV)," presentation to the World Health Assembly, May 23, 2013, slide 2, May 23, 2013, http://www.who.int/csr/disease/coronavirus_infections/WHA_CoV_update_KeijiFukuda_23May13.pdf.

host to the human body; for H7N9, the original source appears to be poultry,⁴ and although the source species for MERS-CoV is unknown at this time, bats are being investigated as a possible source.⁵ With each of these new viruses, health officials now wait to see if either of these viruses will mutate to a point whereby they can sustain human-to-human transmission. If that occurs, then the global community could be in the throes of a pandemic involving a novel virus, or in a worst-case scenario, two separate novel viruses at the same time.

At least one of those threats has been recognized by the Department of Homeland Security (DHS), and is reflected as one of the national planning scenarios listed within that agency's "National Preparedness Guidelines" published in September 2007 (e.g., Scenario # 3: Biological Disease Outbreak—Pandemic Influenza).⁶ The reasoning behind that designation is undoubtedly the specter of a 1918-like pandemic, and rightfully so. That particular strain of type-A influenza managed to inflict a scale of excess mortality and suffering not seen before, and has not been seen since. The book by John M. Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History*, describes the devastation in human life that this "first great collision between nature and modern science" wrought upon humanity in the following way: The influenza pandemic of 1918/1919 "killed more people in a year than the Black Death of the Middle Ages killed in a century; it killed more people in twenty-four weeks than AIDS has killed in twenty-four years."⁷

As a person who spent two tours in central Africa as a Peace Corps Volunteer (PCV) in Gabon from 1998 to 2000, and Kenya in 2001, then later as an epidemiologist,

⁴ Centers for Disease Control and Prevention [CDC], "Avian Influenza A (H7N9) Virus," (n.d.), <http://www.cdc.gov/flu/avianflu/h7n9-virus.htm>.

⁵ Centers for Disease Control and Prevention [CDC], "Middle East Respiratory Syndrome: Frequently Asked Questions/FAQs," (n.d.), <http://www.cdc.gov/coronavirus/mers/faq.html>; Gulfaraz Khan, "A Novel Coronavirus Capable of Lethal Human Infections: An Emerging Picture," *Virology Journal*, 10, no. 66 (2013):5, <http://www.virologyj.com/content/101/1/66>.

⁶ Department of Homeland Security, "National Preparedness Guidelines—September 2007," Appendix B—Capabilities-Based Preparedness Overview, September 2007, http://www.fema.gov/pdf/emergency/nrf/National_Preparedness_Guidelines.pdf, 31.

⁷ John M. Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History* (New York, NY: Penguin Books, Penguin Group, 2004), 5.

that last comparison to Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) truly resonates for those of us there in the late 1990s and early 2000s; a time when that latest plague upon Africa was running amok and left nearly unchecked. For people who witnessed the devastation that HIV/AIDS brought upon Africa at that time, the comparison that Mr. Barry uses is truly awful; for it also provides a contemporary gauge of the scale and suffering wrought upon our great-grandparents by the 1918–1918 influenza pandemic.

When comparing Mr. Barry’s sobering facts with the combat casualties attributed to World War One (approximately 15 million people in four years), against those of the 1918/1919 influenza (estimates of nearly twice that in six months and 50 million overall); it is awe inspiring what a novel virus could inflict upon an unsuspecting and immunologically naïve population.⁸ Science states that these naturally occurring pandemics are both normal, and to some extent, cyclical; it is not a matter of “if” humanity will see this sort of plague revisited, but “when.”⁹

Humanity is somewhat familiar with these natural cycles of pandemics involving type-A influenzas. In the past century alone, four such pandemics have been witnessed with the most recent emerging only four years ago. The first was the 1918 H1N1 “Spanish Influenza” that claimed more than 50 million lives globally (described by the Centers for Disease Control and Prevention (CDC) as a severe pandemic). The second was the 1957 H2N2 “Asian Influenza” that claimed more than one million lives globally (described by the CDC as a moderate pandemic). The third was the 1968 H3N2 ‘Hong Kong’ influenza that claimed more than half a million lives globally (described as a mild pandemic), and most recently, the fourth was the 2009 H1N1 “Swine Flu” that the British

⁸ Karlen, *Man and Microbes: Disease and Plagues in History and Modern Times*, 145; Jeffrey K. Taubenberger and David M. Morens, “1918 Influenza: The Mother of All Pandemics,” *Emerging Infectious Diseases*, 12, no. 1 (January 2006): 20, <http://dx.doi.org/10.3201/eid1209.050979>.

⁹ Jeffrey K. Taubenberger and David M. Morens, “1918 Influenza: The Mother of All Pandemics,” *Emerging Infectious Diseases*, 12, no. 1 (January 2006): 20, <http://dx.doi.org/10.3201/eid1209.050979>.

medical publication, *The Lancet*, calculates to have claimed approximately a half million lives.¹⁰

Compounding that threat, humanity now faces yet another type of virus that has bridged the biological divide between animal species and humans, coronaviruses. As with type-A influenza viruses, these coronaviruses are also derived from common illnesses that mutate to such a point that they develop uncommon capabilities.¹¹ Although many people have, at one time or another, experienced a human coronavirus (HCoV) first-hand (moderate upper-respiratory tract illness commonly called a “cold”), that experience is far different from those observed in 2003–2004 when Severe Acute Respiratory Syndrome (SARS) made its dramatic debut in southeast China. Prior to that epidemic (and since HCoVs were first identified in the mid-1960s) science only knew of two types of human coronaviruses, HCoV-229E and HCoV-OC43.¹² The 2003 SARS event was the first major and global outbreak in the post-September 11 world. When people in southeast China’s Guangdong Province began falling ill in both alarming numbers and with alarming symptoms, public health agencies, such as the World Health Organization (WHO), were prepared to “expect the unexpected.” The October 2001 anthrax letter attacks forced public health and its clinical partners to assume anything when patients present themselves with odd symptomology and age distribution. Yet, even in hindsight, both Chinese public health officials and WHO officials were shocked by what they found; a new and easily transmitted virus between people, who once exposed, would become very ill with far too many dying from complications.¹³

¹⁰ Rachele Salomon and Robert G. Webster, “The Influenza Virus Enigma,” *Cell*, 136 no. 3 (2009): 402–410; Martin I. Meltzer, “Basic Instructions and Template of Draft Report: Using FluAid and FluSurge to Estimate the Potential Impact of the Next Influenza Pandemic upon Locale Y,” *Centers for Disease Control and Prevention [CDC]*, March 22, 2006, <http://www.cdc.gov/flu/pandemic-resources/tools/downloads/pandemic-impact-estimate-instructions.pdf>, 3; Fatimah S. Dawood et al., “Estimated Global Mortality Associated with the First 12 Months of 2009 Pandemic Influenza A H1N1 Virus Circulation: A Modeling Study,” *The Lancet Infectious Diseases* 12, no. 9 (September 2012): 687–695.

¹¹ Centers for Disease Control and Prevention [CDC], Coronavirus Homepage, “About Coronaviruses,” (n.d.), <http://www.cdc.gov/coronavirus/about/index.html>.

¹² L. van der Hoek et al., “Identification of a New Human Coronavirus,” *Nature Medicine* 10, no. 4 (April 2004): 368–373.

¹³ Centers for Disease Control and Prevention [CDC], “Remembering SARS: A Deadly Puzzle and the Efforts to Solve It,” (n.d.), <http://www.cdc.gov/about/history/sars/feature.htm>.

This was humanity's first recorded experience with highly pathogenic coronaviruses, when a regional outbreak raced across Asia, and then the globe. In the eight-month rampage of that novel virus, the WHO calculates that SARS managed to infect a total of 8,098 people worldwide (in 37 countries) with 774 losing their lives to this infection. When the number of SARS-attributed deaths is divided into the total number of confirmed SARS cases, this generates a case fatality rate (CFR) of 9.6 percent. This combination of a novel virus, matched with an impressive transmissibility and high CFR, created a great amount of fear and consternation amongst the global community of public health and healthcare partners.¹⁴

It is against that backdrop that this research focuses on possible pharmaceutical interventions that would help expand the list of options public health could employ in a response. This research explores current and proposed medicines available in the United States (U.S.) medical system's inventory (e.g., Federal Drug Administration [FDA] approved, or pending such an approval) that could help provide a treatment and/or prophylaxis option for pandemic-strain novel viruses. A review of single-medication and multi-medication protocols is researched. An overview of existing literature explains what the current trends and recommendations are amongst clinical researchers addressing novel and pandemic strain viruses (specifically type-A influenzas and HCoV), which is followed by a detailed examination of what science is currently telling the public health community.

The results of this research are intended to meet an identified need by the state of Nevada's Division of Public and Behavioral Health (DPBH) as it continues to prepare for possible future operations against a potential H7N9 and/or MERS Co-V response. Therefore, any calculations or estimates used in this research utilize Nevada-specific data, with any recommendations being intended for implementation within Nevada for its 2.7 million citizens.

The fourth chapter compares what science is recommending against the three criteria that the Nevada DPBH would need met, if it were to select a therapy for an

¹⁴ Centers for Disease Control and Prevention [CDC], "Frequently Asked Questions About SARS," (n.d.), <http://www.cdc.gov/sars/about/faq.pdf>.

expanded state stockpile: medical efficacy, cost, and logistical considerations. The fifth and final chapter summarizes these findings and makes recommendations that fit within the aforementioned criteria.

B. BACKGROUND

1. Lessons from the 1918–1919 Influenza Pandemic

When addressing the threat posed by any novel type-A influenza, the best example is that of the 1918–1919 “Spanish” Influenza (so named because the neutral and uncensored Spanish press was the first to report on this war-time news story).¹⁵ In terms of both its global scale, its excess morbidity (number of people it made very sick), and its excess mortality (the number of people it killed beyond the deaths normally expected from old age, heart attacks, etc.), it is truly the “Mother of All Pandemics.”¹⁶ In researching the literature for this specific pandemic, an abundance of data and analysis exists concerning this global event. As a result of this wealth of information, lessons to be learned from this event could be applied to any and all such future events of this scale and magnitude.

2. Lessons from the 2003–2004 Severe Acute Respiratory Syndrome (SARS) Pandemic

Although this event was caused by a different type of virus (CoV are classified as belonging to the “positive sense single-strand Ribonucleic Acid (RNA) virus” group, and type-A influenzas are classified as belonging to the “negative sense single-strand RNA virus” group within the Baltimore Classification system), it serves as a case-study of how modern public health, on a global scale, responds to completely new viral threats.¹⁷ This event also serves as a study (within the science of communicable diseases) of a

¹⁵ Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History*, 171–172.

¹⁶ Taubenberger and Morens, “1918 Influenza: The Mother of All Pandemics,” 15.

¹⁷ David Baltimore, “Expression of Animal Virus Genomes,” *Bacteriology Reviews* 35, no. 3 (September 1971): 235–241.

phenomenon called “super spreaders” and how a highly pathogenic novel virus can go from a regional issue, to a global crisis, within days to weeks.¹⁸

3. Common Causes of Fatality between the 1918 Influenza and 2003 SARS Outbreaks

Although these two events are separated by 85 years and decades of medical advances, the biological processes that take the lives of those who succumb to either of these illnesses are quite similar. Each of these infections, at their root, are an invasion of a novel virus into the human body’s respiratory system. These two separate infections even share common modes of transmission between cases, referred to as droplet and contact exposures (e.g., droplet exposures occur when the body ejects pathogens by coughing sneezing, and then those fall to the ground, and contact exposures occur when pathogens remain on surfaces that people often touch such as handrails and elevator buttons, and then touch their eyes/nose/mouth). For a significant portion of the total fatalities associated with each of these infections (some researchers have attributed as much as 50%), the cause of death was often described as viral pneumonia (an infection of the lungs that significantly reduces that organ’s ability to provide oxygen to the rest of the body).¹⁹ In the intervening years since the 1918 event, physicians have developed a term for this “pathological process” that “puts extreme stress on the lungs,” called Acute Respiratory Distress Syndrome or ARDS, for short.²⁰ Almost unique to each of the illnesses this thesis reviews, is an over-reaction of an infected body’s immune system to contain and defeat an invading pathogen; this phenomenon is known simply as a “cytokine storm.”²¹ The interplay between exposure, infection, the descent to ARDS, and the resulting cytokine storm, shall be discussed in detail later in this thesis.

¹⁸ Centers for Disease Control and Prevention [CDC], “Remembering SARS: A Deadly Puzzle and the Efforts to Solve It.”

¹⁹ Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History*, 252.

²⁰ Ibid., 250.

²¹ Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History*, 249–251.

4. Public Health Response Options in the Face of a Pandemic

By definition, any novel virus is a biological threat against which humans have very little, or no defense. When faced with a challenge of this type, everyone, to use an old euphemism, is “in the same boat.” A common aspect of pandemics involving novel viruses is that the tools most often relied upon to protect the populace from these biological invaders have basically no effect on them. Current medicines, antibiotics and the medical system become of little value, and are thus forced to return to a model of medicine that resembles that of bygone ages (e.g., isolation and quarantine, etc.). These illnesses are often referred to as “crowd diseases” because they transmit efficiently through densely populated hubs of people.²² In this sense, they are brutally efficient at breaking the social bonds that bring people together: family kinship, friendship, professional colleagues, etc. The bonds are broken when the fear of contracting an illness without any known treatment or vaccination outweighs one of the most primal human needs, being a “social creature.” When the threat feared most can be brought to people by family/friends/acquaintances, then the bonds that hold everyone together can be temporarily torn.²³

Under these conditions, public health is forced to employ strategies that resemble “measures used since antiquity, such as quarantine and social distancing.”²⁴ In the case of the 2003–2004 SARS epidemic, those “measures used since antiquity” worked rather well in some countries (e.g., Vietnam and Canada) and not nearly so well in others (e.g., China). In the case of the 1918–1919 influenza, the impact of those measures varied from town to town, and from city to city.²⁵ State and local health departments wrestle with how to cope with a prolonged pandemic to novel viruses by organizing their response options into various groups, with the state health division in Nevada being no different. In

²² Arno Karlen, *Man and Microbes: Disease and Plagues in History and Modern Times*, 48–49.

²³ Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History*, 336–338.

²⁴ Alexandra Minna Stern, Martin S., Cetron, and Howard Markel, “The 1918–1919 Influenza Pandemic in the United States: Lessons Learned and Challenges Exposed, (Guest Editorial), *Public Health Reports* 125, suppl. 3 (2012): 6.

²⁵ Richard J. Hatchett, Carter E. Mecher, and Marc Lipsitch, “Public Health Interventions and Epidemic Intensity During the 1918 Influenza Pandemic,” in *Proceedings of the National Academy of Sciences [PNAS]* 104, no. 18 (May 1, 2007), www.pnas.org/cgi/doi/10.1073/pnas.0610941104.

the months following the 2009 H1N1 pandemic influenza response, the Nevada public health preparedness (PHP) program developed something called the “Public Health Toolbox” in an effort to help non-public health response partners better understand what public health could “bring to the table.” That “toolbox” is shorthand for a long acronym called the Vaccination, Medication, Antivirals, Isolation, Quarantine, Hygiene, Social Distancing (VMAIQHS) model. This model lists, in order of efficacy, the various interventions that public health could possibly employ to counter a biological threat. The components of this model are as follows.

- Vaccination
- Medication
- Antivirals
- Isolation
- Quarantine
- Hygiene (to include decontamination if applicable and personal protective equipment (PPE))
- Social Distancing

The intent of this research is not to determine if this VMAIQHS model currently used by the state Nevada is valid and/or generalizable; rather, this model is used as an example to help provide the reader with a context of how one state organizes its response options in the face of biological threats.

a. The Prevention-based Model

The aforementioned model used as an example reflects the national focus on preventing an outbreak of disease involving a biological threat, which has been a major cornerstone of the CDC’s Division of Strategic National Stockpile (DSNS) when it developed a “national repository of life-saving pharmaceuticals and medical supplies.”²⁶ In response to the 2009–2010 H1N1 response, many of the processes that states had trained and exercised for were put into action. In April 2009, the CDC released 25% of each state’s allocation of antiviral drugs (e.g., Oseltamivir/Tamiflu and

²⁶ Centers for Disease Control and Prevention [CDC], “A National Repository of Life-Saving Pharmaceuticals and Medical Supplies,” October 2012, <http://www.cdc.gov/phpr/stockpile/stockpile.htm>.

Zanamivir/Relenza), PPE, and respiratory protection devices to help bolster state capabilities in the face of the H1N1 outbreak.²⁷ This large injection of prevention materials have expanded public health's capabilities at the state and local level; and for states like Nevada that did not have a lot of experience with long-term storage of state-level stockpiles, the H1N1 response materials have provided that experience. With the ensuing large-scale deployment by the CDC of an effective vaccination in the autumn of 2009, a large amount of the antiviral medications/PPE/respiratory protection materials from H1N1 remain in state stockpiles to this day (as is the case in Nevada). With the emergence of the concurrent H7N9 and MERS-CoV threats to public health, these existing state stockpiles will be factored into the plans and preparations of state-level public health agencies.

b. The Treatment-based Model

In both the 1918 Influenza and 2003 SARS events, public health was forced to respond without many of the components listed within the VMAIQHS model. Of particular note was the lack of a viable vaccine and lack of any curative medications such as antibiotics or antivirals. With new research revealing breakthrough technologies, and the pharmaceutical industry creating new medications, are options available now that previous generations lacked in 1918, and the current generation lacked during the 2003 SARS outbreak? This research explores possible pharmaceutical solutions that state health departments could stockpile in an effort to expand their current stockpiles and to provide a true "treatment option" in the face of a pandemic response.

C. RESEARCH QUESTION

Are drug therapies (FDA approved or in the pipeline for FDA approval) available that either limit virus replication within a host cell, or reduce the body's hyper-immune response (a.k.a. "cytokine storm," which is a hyper-immune response by the body to an invading pathogen) to novel (pandemic strain) viruses with which states could

²⁷ Centers for Disease Control and Prevention [CDC], "CDC Health Update: Swine Influenza A (H1N1) Update: New Interim Recommendations and Guidance for Health Directors about Strategic National Stockpile Material," distributed via Health Alert Network/HAN on April 26, 2009 at 11:45 PM EST, <http://www.cdc.gov/h1n1flu/HAN/042609.htm>.

supplement their existing stockpiles? This research attempts to identify possible drug therapies against novel and pandemic strain viruses that could be employed within the United States at state-level public health departments. These findings could be used to help state health departments expand their current capabilities from a prevention-based model to include a more robust treatment-based model of response as well.

As potential therapies are revealed, they will then need to fit within three specific criteria for a state health division, such as Nevada's, to purchase them: medical efficacy, cost, and logistical considerations. This research also reviews combining existing drug therapies already stockpiled within state health departments (e.g., antibiotics, antivirals, etc.) with potential therapies revealed in this thesis. The intent is to provide public health leadership at the state level with more options than currently available in the face of a potential pandemic involving any sort of novel virus (such as the H7N9 threat emerging from China and the new MERS-CoV threat emanating from Saudi Arabia).²⁸

²⁸ World Health Organization [WHO], "Avian Influenza A (H7N9) Virus," (n.d.), http://www.who.int/influenza/human_animal_interface/influenza_h7n9/en/; World Health Organization [WHO]. "WHO Statement on the Second Meeting of the International Health Regulations [IHR] Emergency Committee Concerning MERS-CoV," July 17, 2013, http://www.who.int/mediacentre/news/statements/2013/mers_cov_20130717/en/.

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II. LITERATURE REVIEW

The literature review included for this research spans a wide range of publications from a broad selection of resources. While researching two separate epidemics that occurred 85 years apart from each other, special care was given to include a wide sample of texts and articles that span this length of time. As a result, the reader will notice that many of the books and texts cited throughout this research have publication dates that go back as far as 1918. The intent was to capture as much of the “original” data and reporting that government officials published in the months and years following each of these global health events. In addition, these books and texts are intended to help establish the context and framework in which each of these large-scale epidemics occurred, with the hope that they may yield clues as to how to deal with future epidemics of this scale.

Pandemics pose a unique challenge to homeland security practitioners because of their scale, duration, lethality, and sudden onset. These threats are reflected within a series of core homeland security documents: the National Health Security Strategy, the Pandemic and All-Hazards Preparedness Act (PAHPA), the Target Capabilities List (TCL), just to name a few.²⁹ Together these documents (and similar ones) help prevent “black swan” events (a.k.a. events that have low probability of occurring, but high consequence if they do occur) like those of the 1918 Influenza and the 2003 SARS epidemics from fading away in collective memory.³⁰ Based on the fact that pandemic influenza is still listed as third on the national roster of national planning scenarios speaks

²⁹ U.S. Department of Health and Human Services [DHHS], *National Health Security Strategy* (Washington, DC: U.S. Department of Health and Human Services, 2011), <http://www.phe.gov/Preparedness/planning/authority/nhss/Pages/default.aspx>; Govtrack.us, “H.R. 307: Pandemic All-Hazards Preparedness Reauthorization Act of 2013, 113th Congress, 2013–2015, Text as of March 19, 2013,” <http://www.govtrack.us/congress/bills/113/hr307/text>; Federal Emergency Management Agency [FEMA], “Target Capabilities List [TCL],” September 2007, <http://www.fema.gov/pdf/government/training/tcl.pdf>.

³⁰ Nassim N. Taleb, *The Black Swan: The Impact of the Highly Improbable* (New York, NY: Random House Trade Paperback Edition, 2010), 7.

volumes as to how federal, state, and local levels of government perceive this low probability/high consequence threat.³¹

Whereas the books and texts included within this literature review provide a more macro view of the 1918 influenza event, and the 2003 SARS event, the scientific reports and articles help provide a more micro view of trends within the clinical community for possible treatments related to cytokine storm in patients suffering from pandemic strain viruses. In an effort to achieve this goal, this literature review relied on U.S. government articles and reports (e.g., CDC, National Institutes of Health [NIH], etc.), professional journals of U.S. origin, and current scientific research. These resources were identified and located through heavy use of ProQuest and PubMed from the Dudley Knox Library's online system at the Naval Postgraduate School (NPS). As discussed briefly in the introduction to this thesis, the primary focus of this research is to identify possible drug therapies against novel and pandemic strain viruses that could be employed within the United States at state-level public health departments. As a result, non-U.S. texts/research/journals were not used in great numbers for this research. The majority of the references used throughout this research were gleaned from a wide range of books and articles.

A. NOVEL VIRUSES AS A THREAT TO HOMELAND SECURITY

From a Homeland Security perspective, why even study a naturally occurring epidemic like the 1918 Influenza event, or the 2003 SARS event? Surely, more manageable and pragmatic topics exist on which to write a thesis for a school, such as the U.S. Center for Homeland Defense and Security (CHDS). Yet, the research within this thesis has revealed that “diseases have been the biggest killers of people, they have also been decisive shapers of history.”³² As terrible as the casualty counts of America's various conflicts have been, as well as those of terrorist attacks on U.S. citizens, both in

³¹ Federal Emergency Management Agency [FEMA], “National Preparedness Guidelines, Appendix B—Capabilities-Based Preparedness Overview,” September 2007, http://www.fema.gov/pdf/emergency/nrf/National_Preparedness_Guidelines.pdf.

³² Jared Diamond, *Guns, Germs, and Steel: The Fates of Human Societies* (New York, NY: W.W. Norton and Company, Inc., paperback edition, 1999), 197.

this country and abroad; they pale in comparison to the death tolls wrought upon the American people from naturally occurring diseases. Although scientific and medical advances have provided more tools to combat infectious disease, and the “means available to fight disease are infinitely more sophisticated than ever seen in human history,” to this day, this nation is still “uniquely vulnerable to viral diseases.”³³ In spite of all the advances to help prevent diseases and/or cure them, why are “strange new diseases that have leaped up out of nowhere and grabbed the world by the throat” still seen?³⁴

The available literature is both abundant and detailed in describing how novel viruses impact human societies; by their very nature, novel viruses leave bodies unprepared to meet these unfamiliar invaders with their uncommon lethality to immune systems.³⁵ Although plentiful examples of contemporary literature are available on the 1918 Influenza, the most compelling texts come from the people who witnessed that pandemic directly, as either a patient suffering from the illness, or as clinicians trying desperately to aid the afflicted. From the perspective of the patients, perhaps no better example helps describe in excruciating detail what it was like to be ill with the 1918 influenza virus than Katherine Anne Porter’s book *Pale Horse, Pale Rider* originally published in 1939. As a journalist working in Denver, Colorado (in the fall of 1918), Ms. Porter fell ill with influenza and recounts in haunting detail what it was like to be both ill, and near death, with an illness that disabled her for over a month.³⁶ In her book, she describes the physical pain brought on by an infection of this type as such:

Pain returned, a terrible compelling pain running through her veins like heavy fire, the stench of corruption filled her nostrils, the sweetish sickening smell of rotting flesh and pus; she opened her eyes and saw pale

³³ Thomas Abraham, *Twenty-First Century Plague: The Story of SARS* (Baltimore, MD: Johns Hopkins University Press, paperback edition 2007), 14.

³⁴ Ibid., 88.

³⁵ Gina Kolata, “The 1918 Flu Killed Millions: Does it Hold Clues for Today?,” *New York Times*, March 26, 2006, http://www.nytimes.com/learning/teachers/featured_articles/20060328tuesday.html.

³⁶ Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History*, 394.

light through a coarse white cloth over her face, knew that smell of death was in her own body, and struggled to lift her hand.³⁷

Elsewhere in the literature are narratives from the healthcare workers responsible for the care of those like Ms. Porter who were ill with the virus. Although the texts used in this review are replete with vivid descriptions of what it was actually like, perhaps the most poignant were those of Dr. Victor C. Vaughan, Dean of the University of Michigan Medical School, who was called to military service to advise then-U.S. Army Surgeon General William Gorgas. In his book, *A Doctor's Memories* (published in 1926), Dr. Vaughan describes the impact that the 1918 Influenza had on humanity as such:

It encircled the world, visited the remotest corners, taking toll of the most robust, sparing neither soldier nor civilian, and flaunting its red flag in the face of science.³⁸

Common in name only, the symptoms and severity of highly pathogenic influenza viruses, such as the 1918 strain, as well as those of novel HCoV, are far different from the annual inconvenience that many have grown to regard seasonal influenza (or HCoV) to be. When these common viruses mutate to such an extent that they, for reasons still not fully understood, develop uncommon capabilities, modern medicine is left to scramble together a response.

B. CHARACTERISTICS OF PANDEMICS INVOLVING A NOVEL VIRUS

In the two case studies of pandemics used throughout this thesis, four common shared characteristics have been identified, with core lessons being generated that are germane to planning for future pandemics.

The first shared characteristic to each of these epidemics (and perhaps the most obvious) would be the speed by which they circumnavigated the globe. The 1918 influenza took approximately four months to cross the planet, while the 2003 SARS

³⁷ Katherine A. Porter, *Pale Horse, Pale Rider* (New York, NY: Harcourt Brace & Company, 1939), 201.

³⁸ Victor C. Vaughan, *A Doctor's Memories* (Indianapolis, IN: Bobbs-Merrill Company, 1926), 432.

epidemic took a mere 90 days.³⁹ Global air travel has given novel viruses a direct conduit to all the world's major population hubs. The spread and frequency of today's air travel system ensures that a sick person from Hong Kong (to use an example from SARS) could be carried to any point in Southeast Asia within three to four hours, to Europe within 12 hours, and to North America within 18 hours.⁴⁰ As the "global village" continues to grow and expand into areas not previously settled or inhabited by humans, this trend of rising rates of deadly infectious diseases, from previously unknown pathogens, matched with a global travel system, will continue to challenge both homeland security and public health agencies throughout this shared planet.⁴¹

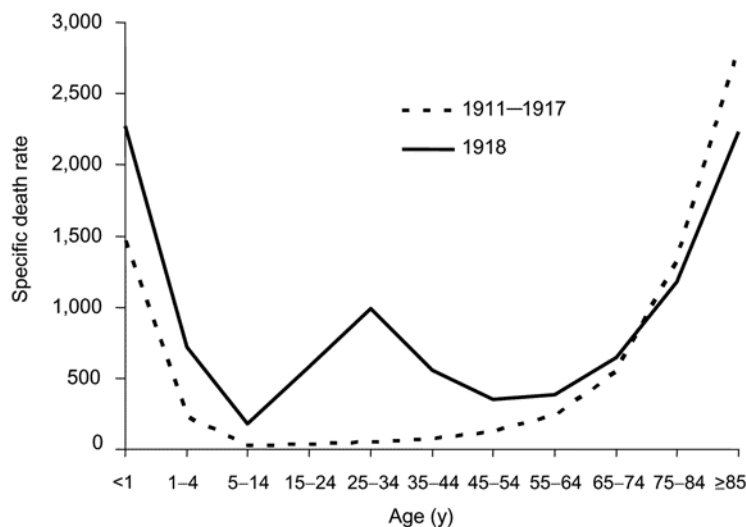


Figure 1. “U-” and “W-” Shaped Combined Influenza and Pneumonia Mortality, by Age at Death, per 100,000 Persons in Each Age Group, United States, 1911–1918. Influenza- and Pneumonia-Specific Death Rates Are Plotted for the Interpandemic Years 1911–1917 (Dashed Line) and for the Pandemic Year (1918) (Solid Line).⁴²

³⁹ Alfred W. Crosby, *America's Forgotten Pandemic: The Influenza of 1918*, 2nd ed. (New York, NY: Cambridge University Press, 2003), 28; Abraham, *Twenty-First Century Plague: The Story of SARS*, VIII.

⁴⁰ Abraham, *Twenty-First Century Plague: The Story of SARS*, 11.

⁴¹ Howard Markel, *When Germs Travel*, 1st ed. (New York, NY: Pantheon Books, 2004), 9.

⁴² Jeffrey K. Taubenberger and David M. Morens, “1918 Influenza: The Mother of All Pandemics,” *U.S. Centers for Disease Control and Prevention [CDC]* 12, no. 1 (January 2006): Figure 2, 19, <http://wwwnc.cdc.gov/eid/article/12/1/05-0979-f2.htm>.

The second characteristic to each of these pandemics are the odd age distribution ranges within a population. These types of pandemic viruses seem to gravitate toward the middle age ranges (e.g., the 20- to 50-year olds). Normally, when a common strain of type-A influenza or coronavirus (CoV) infects humans, illness is often manifested within the younger and older age ranges of a given population since the younger members of the population do not yet have fully developed immune systems, while older members have immune systems that are, generally speaking, on the decline. When plotted on a graph, which is referred to in epidemiology as a U-shaped age distribution of disease, this age range can be seen, as depicted above in Figure 1 from the Taubenberger/Morens article for the 1918 Influenza, and again described in a separate piece, to a lesser extent, for the 2003 SARS event by Liang et al.⁴³ What is observed with pandemic-strain viruses is their unique ability to infect those middle age ranges, thus forming what is called the W-shaped age distribution of illness. An unfortunate aspect to this sort of distribution is the fact that many of the people within the middle age ranges who succumb to their illness, were family members of the ill who tended to their loved one(s), or healthcare workers doing their job to help save lives. Thomas Abraham does a thorough study of this pattern of a novel virus “spreading among hospital workers and close contacts of patients” in his book about the 2003 SARS epidemic.⁴⁴

A third characteristic shared between these two epidemics is the limitation of at least a six- to twelve-month delay from when a novel-strain pandemic begins, and when an effective vaccine strategy is produced and disseminated worldwide.⁴⁵ Thus, one of public health’s most successful “tools” will be unavailable in the opening salvo of a novel virus’ attack on humanity. In light of this reality, a sensible strategy for federal/state/local partners to take would be a delaying action with the intent of preventing the number of

⁴³ Taubenberger and Morens, “1918 Influenza: The Mother of All Pandemics,” Figure 2, 19; W. Liang et al., “Severe Acute Respiratory Syndrome, Beijing, 2003,” *U.S. Centers for Disease Control and Prevention [CDC]* 10, no. 1 (January 2004): Figure 3, 28. <http://wwwnc.cdc.gov/eid/article/10/1/03-0553.htm>.

⁴⁴ Abraham, *Twenty-First Century Plague: The Story of SARS*, 57.

⁴⁵ Elena A. Govorkova and Robert G. Webster, “Combination Pharmaceutical Therapy for Influenza,” *National Center for Biotechnology Information* 2, no. 8 (August 2010): 1510, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3185732/#__ffn_sectitle.

new cases (a.k.a. incidence rate) from increasing exponentially while awaiting a viable vaccine to be developed and distributed.

The fourth and final characteristic of these two pandemics, within the range of this literature review, are the physiological mechanisms that ultimately cause fatality within infected patients, a phenomenon referred to as a “cytokine storm.” In an odd twist, it is not the virus itself that takes the lives of its victims; it is a hyper-immune response that ultimately overwhelms the body of those who succumb. This nuance (as related to pandemic strain viruses) is discussed in detail by Alleva et al. in their article:

It is now generally accepted that the infectious agent in isolation does not cause the illness and fatal outcome seen in acute systemic infectious diseases. Instead, the pathogen induces host cells to generate excessive amounts of pro-inflammatory cytokines...thus generating the disease we observe. This general concept....is now often referred to as the “cytokine storm.”⁴⁶

Under normal conditions, young adults have the most robust immune systems that are often the most capable of repelling an invader, thus making them the healthiest element of the population. Yet, highly pathogenic novel viruses (such as the two described in this thesis) have figured out a way to turn that strength into a weakness:⁴⁷

In 1918 the immune systems of young adults mounted massive responses to the virus. That immune response filled the lungs with fluid and debris, making it impossible for the exchange of oxygen to take place. The immune response killed.⁴⁸

C. SUMMARY

With the planet’s population expected to surpass nine billion people by the year 2050, pandemic strain viruses will continue to emerge as people and populations penetrate into unfamiliar ecosystems and become exposed to new pathogens. From a Homeland Security perspective, these threats will manifest themselves with little

⁴⁶ Lisa M. Alleva, Charles Cai, and Ian A. Clark, “Using Complimentary and Alternative Medicines to Target the Host Response during Severe Influenza,” *Evidence-Based Complementary and Alternative Medicine* 7 no. 4 (2010): 501, <http://dx.doi.org/10.1093/ecam/nep152>.

⁴⁷ Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History*, 249.

⁴⁸ *Ibid.*, 249–250.

warning, and with potentially catastrophic results. With novel viruses being (by definition) completely new to the human immune system, the best defense against them would be vaccination (as per the VMAIQHS model described within the introduction to this thesis). As Thomas Abraham explains in his book about SARS, a delay may occur between the time when a pandemic begins, and the time when an effective vaccine is available:

The only way to prevent an influenza pandemic is through large scale vaccination. Vaccines will have to be tailor-made for any new flu virus, and time as well as money will be a constraint. Developing the vaccine, subjecting it to clinical trials and then getting it ready for commercial production will take at least six months to a year.⁴⁹

In those intervening months, federal, state, and local partners will need to limit the number of new infections with a series of treatment strategies (e.g., using antivirals to help limit a virus' ability to make copies of itself within a host cell, using statins to help limit the body's hyper immune response), and prevention strategies, (e.g., isolation/quarantine/hygiene/PPE/social distancing, collectively known as non-pharmaceutical interventions or NPIs).

This thesis shall focus on expanding the options currently available to state-level governments for treatment strategies, as well as for prophylaxis strategies, in the face of a pandemic strain virus. The hope is to build upon existing state stockpiles of AVs leftover from the 2009 H1N1 pandemic (Tamiflu and Relenza), and to augment those with other pharmaceutical therapies that could be effective against yet-to-be determined novel viruses, would be cost effective, and would fit within Nevada's existing logistics system for bulk storage of medications.

⁴⁹ Abraham, *Twenty-First Century Plague: The Story of SARS*, 140.

III. METHOD

The issue of how governments will respond to pandemics involving a novel virus has received a high level of attention since the identification of a new and highly pathogenic (in other words, it can easily transmit between people and cause appreciable illness within them) avian influenza in the late 1990s identified as H5N1. An explanation of this system to identify new influenza viruses is provided in Chapter IV. From the analysis of data for this thesis, the current body of knowledge surrounding potential treatment options for pandemic-strain viruses appear to focus on two mechanisms to reduce disease in severely ill people, limit virus replication in the host cell, and/or, suppression of the body's hyper-immune response to inhibit the cytokine storm and ARDS. The literature revealed six classes of drugs that have demonstrated an ability either to inhibit virus replication, or to suppress the immune system: antivirals, antibiotics, statins, interferons, corticosteroids, and herbal/alternative medications. With such a wide field of potential therapies, three screening criteria are applied within this analysis chapter and defined as such.

A. MEDICAL EFFICACY

Medical efficacy is defined as a pharmaceutical therapy's ability either to reduce virus replication within a host cell by an appreciable and observable amount, or to reduce the body's immune response by an appreciable and observable amount. Studies involving human subjects are weighted more than those involving animal tests because animal models do not necessarily translate into the human population.

B. COST

Pandemics are by definition, large in scale, and wide ranging. In preparation for any pandemic, projections for how many pharmaceutical therapy doses and regimens should be needed to form a state stockpile would likely be in the tens of thousands. With such a large amount needed, pricing estimates for these therapies need to be no greater than 1% of Nevada's total PHP grant. This percentage is based off what Nevada's PHP program has retrospectively been able to afford, as well as prospective grant funding

estimates. Although national registries provide wholesale price estimates (e.g., a nationally distributed document called the Red Book), access to these sites often require authorization. In an effort to make price quotes cited within this thesis accessible to all readers, an online website called www.GoodRx.com is used to create citable price quotes specific to Nevada's projections for the number of regimens it may need to create a supplemental state stockpile.

C. LOGISTICAL CONSIDERATIONS

With federal grant funding for state-level PHP programs on the decline, state PHP programs, such as Nevada's, will need to rely on its existing climate-controlled bulk-storage warehousing capability. Any potential pharmaceutical therapies revealed by this thesis shall need to fit within Nevada PHP's existing warehouse system (e.g., capable of being stored in climate-controlled facilities long term, no cold-chain requirements, etc.).

With such a wide variety of possible therapies represented within the literature, Table 1 lists those captured within the literature review. Each column is intended to walk the reader through a brief overview of each therapy's major features. The "citations" column provides a synopsis of authors who have conducted related research. The "uses" column describes if the therapy can be used as a prophylaxis (given to people who may have been exposed but have not yet demonstrated any symptoms) and/or as a treatment (people who have been exposed and are demonstrating symptoms). The "pros" and "cons" columns are self explanatory. The "medical efficacy" column describes if the therapy is known to have a positive effect, or if it is still being studied through experimentation. Please keep in mind that "known" therapies may be listed as "experimental" for the simple fact that some old medications are being reviewed for different and innovative new uses. As with almost any medication, long-term immunity is not imparted upon the patient (as would be achieved through immunizations); thus, in an effort to keep the Table 1 from being too crowded, that fact would apply to all listed therapies as a "con."

Table 1. Comparison of Different Therapy Options

Therapy	Citations	Uses	Pros	Cons	Medical Efficacy
Mono-Therapy: Class: Antivirals Oseltamivir (neuraminidase inhibitor)	CDC ⁵⁰ Beigel, Bray ⁵¹ Moscona ⁵² Cooper et al. ⁵³ Treanor et al. ⁵⁴ Nicholson et al. ⁵⁵ Aoki et al. ⁵⁶ Salomon et al. ⁵⁷	Prophylaxis: Yes Treatment: Yes	<ul style="list-style-type: none"> • Already in national/state stockpiles • Familiar to clinicians & public health • Easily stored long term • FDA licensed for influenza type A and B 	<ul style="list-style-type: none"> • Possibly mismatched to virus strain • Drug Resistance • When used as prophylaxis, repeated regimens must be used 	Known: Yes Experimental: No

⁵⁰ Centers for Disease Control and Prevention [CDC], “What You Should Know About Flu Antiviral Drugs,” (n.d.), <http://www.cdc.gov/flu/antivirals/whatyoushould.htm>.

⁵¹ John Beigel and Mike Bray, “Current and Future Antiviral Therapy of Severe Seasonal and Avian Influenza, *Antiviral Research* 78, no. 1 (April 2008): 91–102.

⁵² Anne Moscona, “Neuraminidase Inhibitors for Influenza,” *The New England Journal of Medicine [NEJM]* 353 (September 29, 2005): 1363–1373.

⁵³ Nicola J. Cooper et al., “Effectiveness of Neuraminidase Inhibitors in Treatment and Prevention of Influenza A and B: Systematic Review and Meta-Analysis of Randomized Controlled Trials,” *British Medical Journal [BMJ]*, 326, no. 7401 (June 7, 2003): 1235.

⁵⁴ John J. Treanor et al., “Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza,” *JAMA: the Journal of the American Medical Association* 283, no. 8 (2000): 1016–1024.

⁵⁵ K. G., Nicholson et al., “Efficacy and Safety of Oseltamivir in Treatment of Acute Influenza: A Randomised Controlled Trial,” *The Lancet* 355, no. 9218 (2000): 1845–1850.

⁵⁶ F. Y. Aoki et al., “Early Administration of Oral Oseltamivir Increases the Benefits of Influenza Treatment,” *Journal of Antimicrobial Chemotherapy* 51, no. 1 (2003): 123–129.

⁵⁷ Salomon, and Webster, “The Influenza Virus Enigma,” 402–410.

Therapy	Citations	Uses	Pros	Cons	Medical Efficacy
Mono-Therapy: Class: Antivirals Relenza (neuraminidase inhibitor)	CDC ⁵⁸ Moscona ⁵⁹ Hayden et al. ⁶⁰ Cooper et al. ⁶¹ Makela et al. ⁶²	Prophylaxis: Yes Treatment: Yes	<ul style="list-style-type: none"> • Already in national/state stockpiles • Familiar to clinicians and public health • Easily stored long term • FDA licensed for influenza type A and B 	<ul style="list-style-type: none"> • Mismatched to strain • Drug Resistance • When used as prophylaxis, repeated regimens must be used 	Known: Yes Experimental: No
Mono-Therapy: Class: Antivirals Amantadine (adamantane drug)	CDC ⁶³	Prophylaxis: Yes Treatment: Yes	<ul style="list-style-type: none"> • Affordable • Easily stored long-term 	<ul style="list-style-type: none"> • Only approved for influenza type A • Drug resistance problems 	Known: Yes Experimental: No

⁵⁸ Centers for Disease Control and Prevention [CDC], “What You Should Know About Flu Antiviral Drugs.”

⁵⁹ Moscona, “Neuraminidase Inhibitors for Influenza,” 1363–1373.

⁶⁰ Frederick G. Hayden et al., “Efficacy and Safety of the Neuraminidase Inhibitor Zanamivir in the Treatment of Influenzavirus Infections,” *New England Journal of Medicine* 337, no. 13 (1997): 874–880.

⁶¹ Cooper et al., “Effectiveness of Neuraminidase Inhibitors in Treatment and Prevention of Influenza A and B: Systematic Review and Meta-Analysis of Randomized Controlled Trials,” 1235.

⁶² M. J. Mäkelä et al., “Clinical Efficacy and Safety of the Orally Inhaled Neuraminidase Inhibitor Zanamivir in the Treatment of Influenza: A Randomized, Double-Blind, Placebo-Controlled European Study,” *Journal of Infection* 40, no. 1 (2000): 42–48; Salomon, and Webster, “The Influenza Virus Enigma,” 402–410.

⁶³ Centers for Disease Control and Prevention [CDC], “Influenza Antiviral Drug Resistance,” (n.d.), <http://www.cdc.gov/flu/about/qa/antiviralresistance.htm>.

Therapy	Citations	Uses	Pros	Cons	Medical Efficacy
Mono-Therapy: Class: Antivirals Rimantadine (adamantane drug)	CDC ⁶⁴	Prophylaxis: Yes Treatment: Yes	<ul style="list-style-type: none"> Affordable Easily stored long-term 	<ul style="list-style-type: none"> Only approved for influenza type A Drug resistance problems 	Known: Yes Experimental: No
Mono-Therapy: Class: Antivirals Ribavirin (nucleoside antimetabolite drug)	van Vonderen et al. ⁶⁵ Hayden ⁶⁶ Chan-Tack et al. ⁶⁷ Salomon et al. ⁶⁸	Prophylaxis: Yes Treatment: Yes	<ul style="list-style-type: none"> Easily stored long term Generics available 	<ul style="list-style-type: none"> Not in stockpiles New to public health Can induce anemia and/or toxicity issues 	Known: Yes Experimental: Yes
Mono-Therapy: Class: Antibiotics <u>Fluoroquinolone Class:</u> Ciprofloxacin <u>Tetracycline Class:</u> Doxycycline <u>Penicillin Class:</u> Amoxicillin	Morens et al. ⁶⁹ Wright et al. ⁷⁰	Prophylaxis: Not against viral infection, yes for secondary bacterial infections Treatment: Same as above	<ul style="list-style-type: none"> Already in national stockpiles Familiar to care providers and public Easily stored long term Generics are available and affordable 	<ul style="list-style-type: none"> Only effective against bacterial infections Possible drug resistance issues 	Known: Yes Experimental: No

⁶⁴ Centers for Disease Control and Prevention [CDC], “Influenza Antiviral Drug Resistance.”

⁶⁵ M. G. Van Vonderen et al., “Ribavirin in the Treatment of Severe Acute Respiratory Syndrome (SARS),” *Netherlands Journal of Medicine*, 61, no. 238 (2003): 42.

⁶⁶ Frederick G. Hayden, “Antivirals for Pandemic Influenza,” *Journal of Infectious Diseases* 176, suppl., 1 (1997): S56–S61.

⁶⁷ Kirk M. Chan-Tack, Jeffrey S. Murray, and Debra B. Birnkrant. “Use of Ribavirin to Treat Influenza,” *New England Journal of Medicine* 361, no. 17 (2009): 1713–1714.

⁶⁸ Salomon, and Webster, “The Influenza Virus Enigma,” 402–410.

⁶⁹ David M., Morens, Jeffery K. Taubenberger, and Anthony S. Fauci. “Predominant Role of Bacterial Pneumonia As a Cause of Death in Pandemic Influenza: Implications for Pandemic Influenza Preparedness,” *Journal of Infectious Diseases* 198, no. 7 (2008): 962–970.

⁷⁰ Peter F. Wright, Kathryn B. Kirkland, and John F. Modlin, “When to Consider the Use of Antibiotics in the Treatment of 2009 H1N1 Influenza–Associated Pneumonia,” *New England Journal of Medicine* 361, no. 24 (2009).

Therapy	Citations	Uses	Pros	Cons	Medical Efficacy
Mono-Therapy: Class: Statins Atorvastatin (Lipitor) Rosuvastatin (Crestor) Simvastatin (Zocor)	Fedson ⁷¹ Walsh ⁷² Kumaki et al. ⁷³	Prophylaxis: No Treatment: Yes	<ul style="list-style-type: none"> • Generics are affordable • Readily accessible • Familiar to care givers • Not virus-strain specific 	<ul style="list-style-type: none"> • Some key data linked to animal-only studies 	Known: Yes Experimental: No
Mono-Therapy: Class: Interferons Interferon- α 2b Intron-A	Cinatl et al. ⁷⁴ Katze et al. ⁷⁵	Prophylaxis: No Treatment: Yes	<ul style="list-style-type: none"> • Provide a treatment option if drug resistance issues to AVs arise • Effective against a wide range of influenza viruses 	<ul style="list-style-type: none"> • Expensive • Cold chain issues • Of the three types of interferons (alpha, beta, gamma) alpha primarily affects influenza viruses and beta affects HCoV-Vs 	Known: Yes Experimental: No

⁷¹ David S. Fedson, “Pandemic Influenza: A Potential Role for Statins in Treatment and Prophylaxis,” *Clinical Infectious Diseases* 43, no. 2 (2006): 199–205; David S. Fedson, “Meeting the Challenge of Influenza Pandemic Preparedness in Developing Countries,” *Emerging Infectious Diseases* 15, no. 3 (2009): 365.

⁷² Edward E. Walsh, “Statins and Influenza: Can We Move Forward?,” *Journal of Infectious Diseases* 205, no. 1 (2012): 1–3.

⁷³ Kumaki Yohichi, John D. Morrey, and Dale L. Barnard. “Effect of Statin Treatments on Highly Pathogenic Avian Influenza H5N1, Seasonal and H1N1pdm09 Virus Infections in BALB/c Mice,” *Future Virology* 7, no. 8 (2012): 801–818.

⁷⁴ J. Cinatl et al., “Treatment of SARS with Human Interferons,” *The Lancet* 362, no. 9380 (2003): 293–294.

⁷⁵ Michael G. Katze, Yupeng He, and Michael Gale, “Viruses and Interferon: A Fight for Supremacy,” *Nature Reviews Immunology* 2, no. 9 (2002): 675–687.

Therapy	Citations	Uses	Pros	Cons	Medical Efficacy
Mono-Therapy: Class: Interferons Interferon- α 2b PegIntron	Cinatl et al. ⁷⁶ Katze et al. ⁷⁷	Prophylaxis: No Treatment: Yes	<ul style="list-style-type: none"> • Provide a treatment option if drug resistance issues to AVs arise • Effective against a wide range of viruses 	<ul style="list-style-type: none"> • Expensive • Cold chain issues • Of the three types of interferons (alpha, beta, gamma) only alpha affects influenza viruses and HCo-Vs 	Known: Yes Experimental: No
Mono-Therapy: Class: Interferons Interferon- β 1a Avonex	Hensley et al. ⁷⁸ Morgenstern et al. ⁷⁹	Prophylaxis: No Treatment: Yes	<ul style="list-style-type: none"> • Provide a treatment option if drug resistance issues to other AVs arise • Effective against HCo-V 	<ul style="list-style-type: none"> • Expensive • Cold chain issues • Of the three types of interferons (alpha, beta, gamma) beta impacts HCo-Vs • Small sample size of studies 	Known: Yes Experimental: Yes
Mono-Therapy: Class: Interferons Interferon- β 1a Rebif	Hensley et al. ⁸⁰ Morgenstern et al. ⁸¹	Prophylaxis: No Treatment: Yes	<ul style="list-style-type: none"> • Provide a treatment option if drug resistance issues to other AVs arise • Effective against HCo-V 	<ul style="list-style-type: none"> • Expensive • Cold chain issues • Of the three types of interferons (alpha, beta, gamma) beta impacts HCo-Vs • Small sample size of 	Known: Yes Experimental: Yes

⁷⁶ Cinatl et al., “Treatment of SARS with Human Interferons,” 293–294.

⁷⁷ Katze, He, and Gale, “Viruses and Interferon: A Fight for Supremacy,” 675–687.

⁷⁸ Lisa E. Hensley et al., “Interferon- β 1a and SARS Coronavirus Replication,” *Emerging Infectious Diseases* 10, no. 2 (2004): 317.

⁷⁹ Birgit Morgenstern, Martin Michaelis, Patrick C. Baer, Hans W. Doerr, and Jindrich Cinatl Jr. “Ribavirin and Interferon- β Synergistically Inhibit SARS-Associated Coronavirus Replication in Animal and Human Cell Lines,” *Biochemical and Biophysical Research Communications* 326, no. 4 (2005): 905–908.

⁸⁰ Hensley et al., “Interferon- β 1a and SARS Coronavirus Replication,” 317.

⁸¹ Morgenstern et al., “Ribavirin and Interferon- β Synergistically Inhibit SARS-Associated Coronavirus Replication in Animal and Human Cell Lines,” 905–908.

Therapy	Citations	Uses	Pros	Cons	Medical Efficacy
				studies	
Mono-Therapy: Class: Corticosteroids	Con: Oba ⁸² Pro: Bernard et al. ⁸³ Neutral: Stockman et al. ⁸⁴	Prophylaxis: No Treatment: Yes	<ul style="list-style-type: none"> • Easily accessible • Familiar to clinicians & public health 	<ul style="list-style-type: none"> • Performed poorly against SARS • Limited efficacy overall 	Known: Yes Experimental: No
Mono-Therapy: Class: Herbal medicines	Alleva et al. ⁸⁵ Li et al. ⁸⁶	Prophylaxis: No Treatment: Yes	<ul style="list-style-type: none"> • Useful adjunct treatments • Targets the host response rather than the virus itself 	<ul style="list-style-type: none"> • Not FDA approved • Limited data 	Known: Yes Experimental: Yes
Combo-Therapy: Oseltamivir + Relenza	Govorkova et al. ⁸⁷ Barik ⁸⁸	Prophylaxis: Yes Treatment: Yes	<ul style="list-style-type: none"> • Synergistic effect • Already in national/state stockpiles • Familiar to clinicians & public health • Easily stored long term 	<ul style="list-style-type: none"> • Possible drug resistance issues • When used as an ongoing prophylaxis stockpiles are consumed quickly • Animal models in many studies 	Known: Yes Experimental: Yes
Combo-Therapy:	Govorkova et al. ⁸⁹	Prophylaxis: Yes	<ul style="list-style-type: none"> • Synergistic effect 	<ul style="list-style-type: none"> • Limits virus 	Known: Yes

⁸² Yuji Oba, N. Lee, and J. Sung, “The Use of Corticosteroids in SARS.” *N Engl J Med* 348, no. 20 (2003): 2034–2035.

⁸³ Gordon R. Bernard et al., “High-Dose Corticosteroids in Patients with the Adult Respiratory Distress Syndrome,” *New England Journal of Medicine* 317, no. 25 (1987): 1565–1570.

⁸⁴ Lauren J. Stockman, Richard Bellamy, and Paul Garner, “SARS: Systematic Review of Treatment Effects,” *PLoS medicine* 3, no. 9 (2006): e343.

⁸⁵ Alleva, Cai, and Clark, “Using Complementary and Alternative Medicines to Target the Host Response During Severe Influenza,” 501–510.

⁸⁶ Shi-you Li et al., “Identification of Natural Compounds with Antiviral Activities Against SARS-Associated Coronavirus.” *Antiviral Research* 67, no. 1 (2005): 18–23.

⁸⁷ Govorkova and Webster, “Combination Pharmaceutical Therapy for Influenza,” 1510–1529.

⁸⁸ Sailen Barik, “New Treatments for Influenza,” *BioMed Central [BMC] Medicine* 10, no. 1 (2012): 104.

Therapy	Citations	Uses	Pros	Cons	Medical Efficacy
Oseltamivir + Ribavirin	Barik ⁹⁰	Treatment: Yes	<ul style="list-style-type: none"> Easily stored long term 	<ul style="list-style-type: none"> replication, but has no impact on immune systems' response Ribavirin: causes hemolytic anemia in high doses, high toxicity, and has relatively small therapeutic index 	Experimental: Yes
Combo-Therapy: Relenza + Ribavirin	Govorkova et al. ⁹¹ Barik ⁹²	Prophylaxis: Yes Treatment: Yes	<ul style="list-style-type: none"> Synergistic effect 	<ul style="list-style-type: none"> Limits virus replication, but has no impact on immune systems' response Ribavirin: cause hemolytic anemia in high doses, high toxicity, and has relatively small therapeutic index 	Known: Yes Experimental: Yes
Combo-Therapy: Peramivir + Ribavirin	Govorkova et al. ⁹³	Prophylaxis: Yes Treatment: Yes	<ul style="list-style-type: none"> Synergistic effect 	<ul style="list-style-type: none"> Limits virus replication, but has no impact on immune systems' response Peramivir is approved in Japan and Korea only 	Known: Yes Experimental: Yes (Peramivir is in Phase II trials)

⁸⁹ Sailen Barik, "New Treatments for Influenza," 104.

⁹⁰ Ibid.

⁹¹ Ibid.

⁹² Ibid.

⁹³ Ibid.

Therapy	Citations	Uses	Pros	Cons	Medical Efficacy
Combo-Therapy: Amantadine + Ribavirin	Govorkova et al. ⁹⁴ Barik ⁹⁵	Prophylaxis: Yes Treatment: Yes	<ul style="list-style-type: none"> Enhanced inhibitory effect Synergistic effect 	<ul style="list-style-type: none"> Limits virus replication, but has no impact on immune systems' response Amantadine has been identified to have many drug resistance issues 	Known: Yes Experimental: Yes
Combo-Therapy: Antivirals + Statins	Govorkova et al. ⁹⁶ Barik ⁹⁷	Prophylaxis: Yes Treatment: Yes	<ul style="list-style-type: none"> Addresses virus replication issues and immune system hyper response issues concurrently Some AVs already in state/federal stockpiles Statins are easily accessible and familiar to clinicians 	<ul style="list-style-type: none"> Still being researched and tested Small sample size in some studies Statins are not in SNS/state stockpiles 	Known: Yes Experimental: Yes

⁹⁴ Sailen Barik, "New Treatments for Influenza," 104.

⁹⁵ Ibid.

⁹⁶ Ibid.

⁹⁷ Ibid.

Therapy	Citations	Uses	Pros	Cons	Medical Efficacy
Combo-Therapy: Interferon- α 2b + Ribavirin, PegIntron/Rebetol Combo Pack	Falzarano et al. ⁹⁸	Prophylaxis: Yes Treatment: Yes	<ul style="list-style-type: none"> • Synergistic effect • Proven to have an effect against novel viruses • Provides another Tx option during pandemics • Each component is commonly used in clinic settings 	<ul style="list-style-type: none"> • Comes as an injectable medication only • From SARS: “May improve outcome, but a definitive treatment regimen was not clearly established” (see Falzarano reference) 	Known: Yes Experimental: Yes

⁹⁸ Darryl Falzarano et al., “Inhibition of Novel β Coronavirus Replication by a Combination of Interferon- α 2b and Ribavirin,” *Scientific Reports* 3 (2013).

In Table V in the next chapter, each of these possible options is screened against the three criteria discussed previously: medical efficacy, cost, and logistical considerations.

IV. ANALYSIS

In the face of so much literature on such a timely national and international discussion, what treatment options do states, such as Nevada, have in the face of what appear to be more frequent (and more threatening) pandemics involving novel viruses? Even within the divergent points of view that this research revealed (as well as within those six classes of therapies discussed in the previous section), varying recommendations are provided on if these therapies should be used as a treatment, as a post-exposure prophylaxis (PEP), or as a combination of the two. This chapter then focuses on attempting to untangle some of these recommendations, as well as to find a possible solution that could potentially work for a state, such as Nevada, in its preparations for emerging threats involving novel viruses.

A. VIRAL VERSUS BACTERIAL PNEUMONIA

In the aftermath of global pandemics involving novel viruses, science has explained how these viruses penetrate deep within the human lung and cause significant infection, commonly referred to as pneumonia. The infection of pneumonia to the human body comes in two varieties, viral pneumonia and bacterial pneumonia. Although treatment options were not available in 1918–1919 to counter the effects of either type of pneumonia, detailed records (particularly from the U.S. Army) provide epidemiological data quantifying the number of soldiers and civilians who succumbed to bacterial versus viral pneumonia, or in the parlance of the time, bronchopneumonia versus lobar pneumonia, respectively.⁹⁹ For those who have made the study of pandemic influenza their work, large sources of data support the idea that the majority of deaths attributed to pandemic influenza are caused by viral pneumonia versus bacterial pneumonia, and vice versa. One quote that stands out in support of bacterial pneumonias as the primary cause

⁹⁹ M. W. Ireland [Surgeon General of the U.S. Army] and Joseph F. Siler, *The Medical Department of the United States Army in the World War, Volume IX, Communicable and Other Diseases* (Washington, DC: U.S. Government Printing Office, 1928), 68, (n.d.), <http://ia700303.us.archive.org/13/items/WW1ArmyMedDeptHistV9/WW1ArmyMedDeptHistV9.PDF>; John F. Brundage and G. Dennis Shanks, “Deaths from Bacterial Pneumonia During 1918–19 Influenza Pandemic,” *Emerging Infectious Diseases* 14, no. 8 (2008): 1193.

of death comes from French author, Louis Cruveilhier, in 1919, as he described this interplay of influenza virus infection (or as it is called in French: *la grippe*) and secondary infections caused by opportunistic bacteria that enter the human body: “If grippe condemns, the secondary infections execute.”¹⁰⁰ Picking up from where Monsieur Cruveilhier left off, many highly respected American researchers would also state that opportunistic bacterial pneumonias are the predominant cause of fatality amongst patients suffering from a pandemic strain influenza virus.¹⁰¹ In his book *The Great Influenza*, author John Barry discusses these findings by the Army’s Surgeon General and their implications for today. He writes that the report:

... overstates the proportion of victims who died from Acute Respiratory Distress Syndrome (author’s note: this is referred to as ARDS, which is a consequence of the cytokine storm within a human body)—in effect from influenzal viral pneumonia—because the army study looked only at deaths among soldiers, men who were young and otherwise healthy, the group most likely to have been killed by their own immune systems. In the total population, viral pneumonia and ARDS would not account for as high a percentage of the deaths. Most deaths almost certainly did come from secondary bacterial infections, but probably not quite so many as has been assumed. That should, however, be small comfort for those worry about the next influenza pandemic.¹⁰²

For those who serve within state/local level public health agencies, and are paid to “worry about the next influenza pandemic,” it is the point made by Mr. Barry concerning the “total population” that is of concern, it will be necessary to plan for how to handle both viral pneumonia cases, and bacterial pneumonia cases. In preparation for large-scale biological event, the United States has invested significant time/energy/resources in establishing a strategic national stockpile (SNS). As a result of these preparations, state- and county-level health departments have prepared detailed plans on how they would request, receive, and distribute those federal resources in time of need. A large proportion of the SNS is comprised of antibiotics and antivirals; thus, from a planning perspective,

¹⁰⁰ L. Cruveilhier, *Action du sérum antipneumococcique au cours de la pneumonie et dans les complications de la grippe*, *Annals de l’Institut Pasteur* 33 (1919): 448.

¹⁰¹ Morens, Taubenberger, and Fauci, “Predominant Role of Bacterial Pneumonia As a Cause of Death in Pandemic Influenza,” 962–970.

¹⁰² Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History*, 252.

state and local public health agencies would likely have access to this national asset that could assist them with bacterial pneumonia cases by providing the requisite antibiotics. When combining the stockpiles of these life saving medications with the existing state stockpiles of antivirals discussed previously in this thesis (at both the state and federal levels of government), then state and local health agencies are much better prepared to meet the challenge of treating viral and/or bacterial pneumonia caused by a pandemic strain of virus than this nation's forefathers were in 1918. However, as useful as existing stockpiles may be in treating or preventing bacterial pneumonia cases, public health and its healthcare partners must still be prepared to treat and prevent cases of viral pneumonia as well.

B. CALCULATING THE GROSS ATTACK RATE, HOSPITALIZATION RATE, AND MORTALITY RATE ASSOCIATED WITH A PANDEMIC STRAIN VIRUS

From a state planning perspective, what are the numbers that should be anticipated when preparing for a pandemic involving a novel virus? In the spring of 2013 (following the Nevada Division of Public and Behavioral Health's activation of its planning section for a potential MERS-CoV and/or H7N9 type-A influenza response) the following questions were posed by the state health officer to the state planning section chief.

- How many Nevadan's are expected to fall clinically ill from a novel influenza virus (known within public health as the "Gross Attack Rate" or GAR)?
 - As per the CDC's FluAid 2.0 website, clinical illness is defined as a case of influenza that causes some measureable economic impact, such as one-half day of work lost or a visit to a physician's office¹⁰³
- Of those people who fall clinically ill, how many would require hospitalization (known within public health as the "hospitalization rate")?
- Of those people who fall clinically ill, how many would lose their lives from the illness (known within public health as the "Mortality Rate")?

¹⁰³ Centers for Disease Control and Prevention [CDC], "FluAid 2.0 Pandemic Influenza Planning Resources," (n.d.), <http://www.cdc.gov/flu/pandemic-resources/tools/fluaid.htm>.

Fortunately, for state and local public health planners, researchers at the CDC have provided a useful tool to assist in these calculations by providing national estimates for various rates, via the CDC's FluAid 2.0 downloadable software.¹⁰⁴ In an effort to answer the state health officer's three questions in the spring of 2013, that software was used to calculate these three rates using the following steps.

- Step One: establish what the state of Nevada's total population would be, based off the most recent estimates by the state demographer's office. In Nevada, that estimated number for 2013 is 2,775,216 (as of October 1, 2013).¹⁰⁵ This state demographer's report also splits these total population data into three age ranges as follows:

0 to 19 year olds:	766,414	(27.6% of the state population)
20 to 64 year olds:	1,656,765	(59.7% of the state population)
65+ year olds:	352,038	(12.7% of the state population)
TOTAL:	2,775,216	(100% of the state population)

Note to Reader: Please keep these three numbers (e.g., 766K, 1.6M, and 352K) in mind as they will later be used in Step #3

- Step Two: involves using the CDC software's three GAR ranges listed on page seven of nine on the FluAid 2.0 software. The system instructs planners to calculate for a "lowest" GAR of 15%, a "middle" GAR of 25%, and a "highest" GAR of 35% for a severe strain virus.¹⁰⁶ When these three GAR estimates are applied to the state population of 2,775,216, the following range of gross attack rates are calculated:

15% of 2,775,216	= approximately 416,200 Nevadans may fall ill
25% of 2,775,216	= approximately 693,800 Nevadans may fall ill
35% of 2,775,216	= approximately 971,300 Nevadans may fall ill

¹⁰⁴ Centers for Disease Control and Prevention [CDC], "FluAid 2.0 Pandemic Influenza Planning Resources."

¹⁰⁵ Jeff Hardcastle, "Nevada County Age, Sex, Race, and Hispanic Origin Estimates and Projections 2000 to 2032: Estimates from 2000 to 2012 and Projections from 2013 to 2032," *The Nevada State Demographer's Office*, 5, <http://nvdemography.org/wp-content/uploads/2013/10/Nevada-Summary-Workbook-ASRHO-Estimates-and-Projections-2000-to-2032.pdf>.

¹⁰⁶ Centers for Disease Control and Prevention [CDC], "FluAid 2.0: Estimating State Level Impact of Pandemic Influenza—[Gross Attack Rates], Seven of Nine," <http://www.cdc.gov/flu/pandemic-resources/tools/fluaid.htm>.

- Step Three: calculate the hospitalization rate, which is more challenging to discern for two reasons, 1) the Nevada state demographer’s data covers an age range of zero to 19 years (0 to 19); whereas, the CDC FluAid 2.0 software employs an age range of zero to 18 (0 to 18), and 2) the CDC’s software splits its calculations for this rate into two sub-categories (high risk and non-high risk), then goes on to split those into three sub-tiers of risk (minimum, mean, and maximum). Table 2 lists the FluAid 2.0 estimates for hospitalization rates (listed as rates per 1,000 population of an age range-specific population) as they would appear for any state using this software as a planning tool.

Table 2. Hospitalization Rate Estimates for Nevada during a Pandemic

High Risk	Minimum	Mean (Most Likely)	Maximum
0–18 yrs	2.1%	2.9%	9%
19–64 yrs	0.83%	2.99%	5.14%
65+ yrs	4%	8.5%	13%
Non High Risk	Minimum	Mean (Most Likely)	Maximum
0–18 yrs	0.2%	0.5%	2.9%
19–64 yrs	0.18%	1.46%	2.75%
65+ yrs	1.5%	2.25%	3%
Note 1: Default values are national estimates			
Note 2: Hospitalization rates per 1,000 population by age and risk group			

For the first issue of the demographer’s age range versus that of the CDC’s software, the state data’s age range of “0 to 19 year olds” will be inserted into the CDC’s age range of “0 to 18 year olds.” This decision is based on the fact that the hospitalization rate calculations required for this thesis are macro in nature; thus, little benefit is to be gained by splitting out the 19-year olds from the age group used for the state data.

This second issue of the FluAid 2.0 software splitting the population into two sub-categories (high risk and non-high risk), and then further splitting those into sub-tiers, presents some challenges for state planners. First, if it is known how many people are in each age group, then would it be possible to calculate how many of those people would be considered “high risk” versus “non-high risk?” This is a challenging question for many reasons, and one that has confounded many scientists who have confronted these types of planning scenarios. Fortunately, for state-level planners, the CDC has helped

provide some answers to these questions (as well as guidance), most notably from an article published in 1999 by Meltzer, Cox and Fukuda.¹⁰⁷

As per the CDC’s FluAid 2.0 website, this article was published to provide “a range of national estimates of the number of deaths, hospitalizations, outpatient visits, and those who will become ill but not seek medical care.”¹⁰⁸ The estimates included within the Meltzer et al. article serve as a foundation for the CDC’s FluAid 2.0 software, which in turn helps provide state planners with national estimates as to how many people within each age group would be considered high risk versus non-high risk during a pandemic. Table 1 of the Meltzer et al., article provides the following estimates for the United States.¹⁰⁹

Table 3. Estimate of Age Distribution of Cases and Percentage of Population at High Risk Used to Examine the Impact of Pandemic Influenza in the United States

Age Group (yrs)	Percentage of all cases ^a
0–19	40.0
20–64	53.1
65+	6.8
Totals ^b	100.0
	Percentage at high risk ^c
0–19	6.4
20–64	14.4
65+	40.0
U.S. average ^d	15.4

^aThe actual number of cases will depend upon the assumed gross attack rate. The distribution of cases was based on lower and upper estimates of age-specific attack rates from the 1918, 1928–29, and 1957 epidemics and pandemics.

^bTotals do not add to exactly 100% because of rounding.

¹⁰⁷ Meltzer, Cox, and Fukuda, “The Economic Impact of Pandemic Influenza in the United States: Priorities for Intervention,” 659–671.

¹⁰⁸ Centers for Disease Control and Prevention [CDC], “Seasonal Influenza (Flu),” (n.d.), <http://www.cdc.gov/flu/pandemic-resources/tools/fluaid.htm>.

¹⁰⁹ Meltzer, Cox, and Fukuda, “The Economic Impact of Pandemic Influenza in the United States: Priorities for Intervention,” 660.

^cPersons are categorized at high risk if they have a preexisting medical condition that makes them more susceptible to influenza-related complications. The percentages of age groups at high risk were obtained from the Working Group on Influenza Pandemic Preparedness (GrIPPE, unpub. data). The Advisory Committee on Immunization Practices estimates that 27 to 31 million persons aged <65 years are at high risk for influenza-associated complications.

^dAverage is an age-weighted average, using each age group's proportion of the total U.S. population.

Although those three estimates for high risk are intended to provide a U.S. average, they are nonetheless useful for state planners as well. In the case of Nevada, each of those percentages can be multiplied by its corresponding age category populations, and thus, yield the following results.

6.4% of Nevada's 0 to 19 year olds (766,414) would be considered "High Risk"	= 49,000
14.4% of Nevada's 20 to 64 year olds (1,656,765) would be considered "High Risk"	= 238,500
40% of Nevada's 65+ year olds (352,038) would be considered "High Risk"	= 140,800
Total Number of Nevadans who would be considered 'High Risk'	= 428,300

Table 4 employs the FluAid 2.0 national estimates for hospitalization rates (listed as rates per 1,000 population of an age range-specific population) as they would appear for the state of Nevada on page five of nine of FluAid 2.0's software, under the title of "Estimating State Level Impact of Pandemic Influenza-[Hospitalization]."

Table 4. Hospitalization Rate Calculations for Nevada during a Pandemic

High Risk	Minimum	Mean (Most Likely)	Maximum
0–18 yrs	2.1% of 49K = 103	2.9% of 49K = 142	9% of 49K = 441
19–64 yrs	.83% of 238.5K = 198	2.99% of 238.5K = 713	5.14% of 238.5K = 1,226
65+ yrs	4% of 140.8K = 563	8.5% of 140.8K = 1,197	13% of 140.8K = 1,830
Non High Risk	Minimum	Mean (Most Likely)	Maximum
0–18 yrs	.2% of 766K = 153	.5% of 766K = 383	2.9% of 766K = 2,221
19–64 yrs	.18% of 1.66M = 300	1.47% of 1.66M = 2,440	2.75% of 1.66M = 4,565
65+ yrs	1.5% of 352K = 528	2.25% of 352K = 792	3% of 352K = 1,056
Totals by Age Range	Minimum	Mean (Most Likely)	Maximum
0–18 yrs	103 + 153 = 256	142 + 383 = 525	441 + 2,221 = 2,662
19–64 yrs	198 + 300 = 498	713 + 2,440 = 3,153	1,226 + 4,565 = 5,791
65+ yrs	563 + 528 = 1,091	1,197 + 792 = 1,989	1,830 + 1,056 = 2,886
Totals for <u>All</u> Ages	Minimum	Mean (Most Likely)	Maximum
0–65+ yrs	256+498+1,091 = 1,845 hospitalizations	525+3,153+1,989 = 5,667 hospitalizations	2,662+5,791+2,886 = 11,339 hospitalizations
Note 1: Default values are national estimates			
Note 2: Hospitalization rates per 1,000 population by age and risk group			

- Step Four: calculate the mortality rate, which follows the same methodology used in the hospitalization rate calculations described above. Table 5 employs the FluAid 2.0 national estimates for mortality (aka death) rates (listed as rates per 1,000 population of an age range-specific population) as they would appear for the state of Nevada on page four of nine under “Estimating State Level Impact of Pandemic Influenza–[Deaths].”

Table 5. Mortality Rate Calculations for Nevada during a Pandemic

High Risk	Minimum	Mean (Most Likely)	Maximum
0–18 yrs	.126% of 49K = 6	.22% of 49K = 11	7.65% of 49K = 375
19–64 yrs	.1% of 238.5K = 24	2.91% of 238.5K = 694	5.72% of 238.5K = 1,364
65+ yrs	2.76% of 140.8K = 389	4.195% of 140.8K = 590	5.63% of 140.8K = 793
Non High Risk	Minimum	Mean (Most Likely)	Maximum
0–18 yrs	.014% of 766K = 11	.024% of 766K = 18	.125% of 766K = 96
19–64 yrs	.025% of 1.6M = 40	.037% of 1.6M = 59	.09% of 1.6M = 144
65+ yrs	.28% of 352K = 99	.42% of 352K = 148	.54% of 352K = 190
Totals by Age Range	Minimum	Mean (Most Likely)	Maximum
0–18 yrs	6 + 11 = 17	11 + 18 = 29	375 + 96 = 471
19–64 yrs	24 + 40 = 64	694 + 59 = 753	1,364 + 144 = 1,508
65+ yrs	389 + 99 = 488	590 + 148 = 738	793 + 190 = 983
Totals for All Ages	Minimum	Mean (Most Likely)	Maximum
0–65+	17+64+488 = 569 excess deaths	29+753+738 = 1,520 excess deaths	471+1,508+983 = 2,962 excess deaths
Note 1: Default values are national estimates			
Note 2: Mortality rates per 1,000 population by age and risk group			

C. EMPLOYING RATE CALCULATIONS TO DETERMINE THE SIZE OF A STATE STOCKPILE

The previous section of this chapter described the process of how a state-level PHP program could possibly calculate the gross attack rate, the hospitalization rate, and the mortality rate associated with a pandemic. Although this thesis addresses pandemics involving novel type-A influenzas, or novel human coronaviruses (HCo-V), the CDC FluAid 2.0 software used in the previous section is specific for pandemic influenzas only. Without any such companion software system focused on a novel HCo-V, the estimates generated by the FluAid 2.0 software for influenza pandemics will have to substitute for

pandemics involving a novel HCoV, as well. This is based off of the planning assumption that estimates generated for influenza pandemic planning would be similar with those needed for a pandemic involving a novel HCoV.

Thus, of the three rates calculated in the previous section, which of those should be used to calculate the quantity of a drug therapy to be purchased to create (or supplement) a state stockpile (assuming this thesis finds such a therapy or therapies)? The GAR provides an idea of the total number of people who may fall ill from a novel virus, but as with any virus (novel or otherwise) the range of “illness” can span anything from “barely noticeable” to “life threatening.” This disparity in range can be attributed to epidemiological factors, such as dose exposure, route of exposure, and underlying morbidities (e.g., asthma, pregnancy, chronic obstructive pulmonary disease (COPD), etc.). Although the GAR is a useful planning tool, it may include too large a segment of the population to be of any real use.

The hospitalization rate calculation narrows the focus from those rather large numbers provided in the GAR calculations in step one of the previous section, for example: 15% of Nevadans (a.k.a. 416,200 people) may fall ill, etc. Of the people who fall ill, most interest would be focused on providing potentially life-saving medications to those who are ill enough to require hospitalization. While an underestimate of those seeking treatment, but given the limited response capabilities projected, it would not be unreasonable to restrict treatment to this group.

The mortality rate calculations are useful in that they describe how many people could be lost if nothing is done. From a state-level planning perspective, they are helpful, but perhaps too narrow. They describe a possible result of infection, in this case death, that is hoped to be avoided. As with any drug therapy, it would be necessary to introduce these interventions prior to a patient’s death; thus, from a planning perspective, perhaps this rate is too narrow and too late in the progression of disease.

Therefore, of the three rate calculations described above (GAR, hospitalization, mortality), which should be used to help guide the decision-making process for how much of a drug therapy should be purchased? The hospitalization rate calculations have

been selected for use in determining the quantity of a therapy Nevada should purchase (assuming one is identified later in this thesis). This rate calculation was chosen for this research because it offers a wide enough aperture through which to guide state-level planning estimates, and it assumes that patients who are ill enough to be hospitalized will be in a clinical environment whereby potential drug therapies may be administered properly. In other words, should this thesis identify a possible drug therapy that works very well, yet needs to be administered through an intravenous line (IV), then that may be of little help to patients who are ill, but remain at home, and have no one to open and maintain an IV line for them.

The hospitalization rate calculation also provides a range (e.g., minimum, mean, and maximum) for state-level planners to choose from: minimum is 1,845, mean is 5,667, and, maximum is 11,339. This range provides some latitude for public health leadership when it decides on how and where to spend decreasing budget dollars on a possible state stockpile of new drug therapies.

D. OVERVIEW OF THE SIX CLASSES OF DRUG THERAPIES

For the non-public health disciplines reading this thesis, a brief explanation of each class of medications may be necessary, as well as a brief description of the benefit provided during a pandemic response.

1. Antiviral Medications

The following is a brief explanation of what antivirals are and how they impact a virus' ability to enter or exit a host cell. When an invading virus approaches a possible host cell, it needs a "key" to enter the host cell's outer wall. This process is achieved by a protein on the virus' surface called hemagglutinin; or as the reader may be more familiar with, H (a.k.a. HA). Influenza viruses have 16 of these H proteins on their surface; thus, from the virus' perspective, they have 16 possible "keys" to try upon the host cell's outer wall. In essence, the virus sticks each of these 16 "keys" into receptor sites on the host cell's outer wall one at a time. If the correct "key" is matched to the correct "keyhole," then the virus is allowed to open and pass through the cell's outer wall. Once that happens, the invading virus then hijacks the host cell's replication system and makes

thousands (to millions) of copies of itself, which usually results in the host cell's death. When that process is complete, those new copies of the virus once again need to pass through the outer wall of the host virus, except this time, they need to go from the inside of the cell to the outside of the cell. To achieve that goal, each virus has another set of surface proteins called neuraminidase, or as the reader may be more familiar with, N (a.k.a. NA). Influenza viruses have 9 of these N proteins on their surface; thus, from their perspective, they have nine possible "keys" to try from within the host cell's outer wall. When the CDC or WHO is heard discussing an influenza as "H5N1," they are basically talking about that specific influenza virus' need to fit the fifth (H5) "key" to enter a host cell, and the first (N1) "key" to exit that host cell.

Antivirals work by either blocking some or all of the 16 H "keyholes" (a.k.a. hemagglutinin inhibitors), or some or all of the nine neuraminidase "keyholes" (a.k.a. neuraminidase inhibitors). This process helps to limit virus replication (as was briefly discussed previously in this thesis), and thus, lowering, or nearly cancelling, host cell infection. The current stockpiles of Oseltamivir/Tamiflu and Zanamivir/Relenza are good examples of neuraminidase inhibitors (that work against both type-A and type-B influenza viruses).¹¹⁰ Antivirals often need to be matched to a specific strain of virus, and do not offer permanent protection (a.k.a. immunity) if taken as a prophylaxis (e.g., taken by a person who was exposed but not yet demonstrating any symptoms of illness). This concept has been a key message used by public health educators in explaining these features of antivirals to both the public, and to public health's response partners.

2. Antibiotic Medications

Antibiotic medications were discovered accidentally in 1928 by Scottish biologist, Sir Alexander Fleming, when glass plates he had used for experiments developed a mold. Dr. Fleming noticed that bacteria near the edges of the mold had died off. Further analysis revealed a bacteria-killing substance within the mold later identified as penicillin. This discovery, and the new class of drugs it introduced, helped to both

¹¹⁰ Centers for Disease Control and Prevention [CDC], "Influenza Antiviral Medications: Summary for Clinicians," (n.d.), <http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm>.

revolutionize and transform all of medicine. This advance is due to the fact that antibiotics helped to provide the first real tool against bacterial infection. Age-old bacterial foes, such as plague, etc., were brought under control by this “wonder drug” as it was initially called. Although antibiotics have no effect upon viruses, they remain a useful tool for both clinicians and public health officials in countering opportunistic bacterial infections. Unfortunately, some bacteria have developed resistance to certain antibiotics, and thus, create a threat to global public health.¹¹¹ Although it has no impact on virus replication, nor suppression of the body’s immune response, this class of drugs does have a drastic effect on bacterial infections that often accompany viral infections associated with novel and pandemic strain viruses. As Morens et al. describe in their article about the 1918 influenza pandemic:

Many excess deaths in the 1918 pandemic resulted from a disease process that began with a severe viral infection that spread cell-to-cell down the respiratory tract, causing severe tissue damage but normally followed by prompt tissue repair unless secondary bacterial invasion ensued. The bronchial tree appeared to be the primary organ of involvement in severe 1918 influenza cases; when bacterial invaders in the nasopharynx gained access to the peripheral bronchial tree by direct extension along denuded bronchial epithelium, bronchopneumonia could then occur.¹¹²

3. Statin Medications

Most would recognize statins for their traditional role in lowering cholesterol in the bloodstream. Many would have probably heard of certain brand names for statins, such as Pfizer’s Lipitor or Crestor by AstraZeneca, just to name a few. In addition to their ability to lower cholesterol, statins also have both an anti-inflammatory and an immune-modulatory effect. It is these additional benefits to the use of statins that authors like

¹¹¹ Centers for Disease Control and Prevention [CDC], “Antibiotics Aren’t Always the Answer,” (n.d.), <http://www.cdc.gov/Features/GetSmart/>; Public Broadcasting Service [PBS], “Hunting the Nightmare Bacteria,” *Frontline PBS*, October 22, 2013, <http://www.pbs.org/wgbh/pages/frontline/hunting-the-nightmare-bacteria/>.

¹¹² David M. Morens et al., “The 1918 Influenza Pandemic: Lessons for 2009 and the Future,” *Critical Care Medicine* 38, no. 4 suppl. (2010): e10.

Fedson, Vandermeer, and Walsh discuss in relation to pandemic strain influenzas.¹¹³ Statins do not impact virus replication, yet they do help to suppress the body's immune response. As a class of drugs, they are familiar to medical providers, come in plentiful supply, are affordable, and are easily stored long term, thus making each of these traits an appealing prospect for a state-level stockpile.

4. Interferon Medications

Although interferons would technically be listed as antivirals, they have been separated from that class listed above because their mode of action is so different. These naturally-occurring proteins are made and secreted by the cells of the body's immune system, they are a major type of cytokine, and come in three classes: alpha (helps to treat cancers and viral infections), beta (helps to treat multiple sclerosis), and gamma (helps for treating chronic granulomatous disease).¹¹⁴ Each of these three classes has their own individual effects, as well as overlapping effects, which the MedicineNet.com website describes as, "the mechanism of action of interferon is complex and is not well understood." This class of medications helps to modulate the body's immune system response to challenges from viruses, bacteria, cancers, and foreign substances that impact the body.¹¹⁵ Although interferon alphas do not directly kill viruses, they do help to boost the body's immune system, and to prevent a hyper response by that system.¹¹⁶ More commonly discussed as a treatment for diseases, such as leukemia, AIDS-related Kaposi's sarcoma, chronic hepatitis B and C, the literature review for this thesis generated a large amount of information about using interferon to enhance the body's

¹¹³ Fedson, "Pandemic Influenza: A Potential Role for Statins in Treatment and Prophylaxis," 199–205; Meredith L. Vandermeer et al., "Association Between Use of Statins and Mortality Among Patients Hospitalized with Laboratory-Confirmed Influenza Virus Infections: A Multistate Study," *Journal of Infectious Diseases* 205, no. 1 (2012): 13–19; Walsh, "Statins and Influenza: Can We Move Forward?," 1–3.

¹¹⁴ MedicineNet, "Interferon," (n.d.), <http://www.medicinenet.com/interferon/article.htm>.

¹¹⁵ Ibid.

¹¹⁶ Ibid.

immune system against pandemic strain influenzas, as well as novel HCoV-Vs (specifically interferon- α 2b).¹¹⁷

5. Corticosteroid Medications

This class of medication is similar to the natural hormones produced within bodies that help to control many important functions, such as blood sugar levels, salt levels, as well as the immune system's function.¹¹⁸ These medications are often used to help treat diseases that cause inflammation, as novel viruses would most likely cause within the human lung following infection.¹¹⁹ This class of medication works by blocking substances within the human body that cause swelling. During the 2003–2004 SARS epidemic, these medications fell out of favor because it suppressed the entire immune system; both the good and the bad components of that system's response.

6. Herbal/Alternate Medications

The literature often describes these medications as being “complementary” and “anti-inflammatory” in nature; with their effects primarily targeted on the host response rather than the virus replication.¹²⁰ The Alleva et al. article includes a long list of Chinese herbs often described as “adjunct treatment therapies” to antivirals. Although these herbal medications are not currently licensed within the United States, they do warrant further research and analysis.

E. ANALYSIS OF OPTIONS GENERATED BY THESIS RESEARCH

With such a wide field of possible treatment therapies discussed throughout the literature, which of these could potentially fit within the three criteria employed for this thesis: medical efficacy; cost; and, logistical considerations? In this final section to the

¹¹⁷ Falzarano et al., “Inhibition of Novel β Coronavirus Replication by a Combination of Interferon- α 2b and Ribavirin.”

¹¹⁸ A. C. Poinier and S. M. Shoor, “Corticosteroids,” *WebMD*, May 7, 2010, <http://www.webmd.com/hw-popup/corticosteroids>.

¹¹⁹ *Ibid.*

¹²⁰ Alleva, Cai, and Clark, “Using Complementary and Alternative Medicines to Target the Host Response During Severe Influenza,” 501–510.

analysis chapter, each of the therapies listed in the methods chapter will be screened against these three criteria. In Table 6, the columns are intended to walk the reader through a brief overview of each therapy’s ability to meet each of the three criteria. The “Medical Efficacy” column will provide a simple “yes” or “no” synopsis of what the literature describes for that specific therapy’s ability to: 1) reduce virus replication (listed as ↓ Virus Rep. in the table), 2) reduce the body’s immune response (listed as ↓ Imm. Res. in the table), or 3) have some other effect (e.g., treat secondary infections, etc., listed as other in the table). The “cost” column will begin by employing the three hospitalization rates calculated previously in this chapter (e.g., minimum of 1,845, mean of 5,667, and maximum of 11,339), and then multiply each of those by the price listed within the GoodRx website for that specific therapy. Since these calculations are for strains of virus that may not yet even exist, it is a challenge to forecast a specific treatment regimen (e.g., two 40mg pills per day for 10 days, etc.). In those instances when the GoodRx website does not provide a specific multiday regimen, a generic “one pill/capsule per day for 10 days” treatment regimen will be substituted to allow the website’s required data fields to be populated with a value. The choice of using a 10-day regimen also helps keep the calculations simple. The column listed as “logistical considerations” will describe if a therapy can be held in a warehouse as bulk storage, with no special temperature considerations other than a climate-controlled space (listed as bulk store in the table), or if it will require refrigeration (listed as cold chain in the table). The “citations” column will provide any specific information on where cost estimates were obtained. The final column, listed as a question, will provide the simple “yes” or “no” as to if a specified therapy could be used to build (or supplement) a state-level stockpile. Examples of what could exclude a candidate therapy would be expense (e.g., more than 1% of the state’s annual PHP budget), a cold chain requirement (the state can only handle bulk storage in a climate-controlled warehouse, not in large refrigerators, etc.), or the proposed therapy is already included and widely available through the SNS.

Table 6. Candidate Therapy Selection

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
Mono-Therapy: Antiviral/Oseltamivir (neuraminidase inhibitor)	↓ Virus Rep.: Yes ↓ Imm. Res.: No Other: N/A	1,845= \$202K 5,667= \$620K 11,339= \$1.24M	Bulk Store: Yes Cold Chain: No	GoodRx.com used, Tamiflu brand name, dose pack of 10 capsules of 75mg each <ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens¹²¹ • Price quote for 5,667 ten-day regimens¹²² • Price quote for 11,339 ten-day regimens¹²³ 	No
Mono-Therapy: Antiviral/Relenza (neuraminidase inhibitor)	↓ Virus Rep: Yes ↓ Imm. Resp: No Other: N/A	1,845= \$118K 5,667= \$364K 11,339= \$728K	Bulk Store: Yes Cold Chain: No	GoodRx.com used, relenza brand name, inhaler, 5mg each <ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens of inhalers¹²⁴ • Price quote for 5,667 ten-day regimens of 	No

¹²¹ GoodRx.com, “Tamiflu,” (n.d.), <http://www.goodrx.com/tamiflu/price#/?distance=13&filter-location=&coords=&label=Tamiflu&form=dose+pack&strength=10+capsules+of+75mg&quantity=custom&qty-custom=1845&language=&store-chain=>.

¹²² GoodRx.com, “Tamiflu,” (n.d.), <http://www.goodrx.com/tamiflu/price#/?distance=13&filter-location=&coords=&label=Tamiflu&form=dose+pack&strength=10+capsules+of+75mg&quantity=custom&qty-custom=5667&language=&store-chain=>.

¹²³ GoodRx.com, “Tamiflu,” (n.d.), <http://www.goodrx.com/tamiflu/price#/?distance=13&filter-location=&coords=&label=Tamiflu&form=dose+pack&strength=10+capsules+of+75mg&quantity=custom&qty-custom=11339&language=&store-chain=>.

¹²⁴ GoodRx.com, “Relenza,” (n.d.), <http://www.goodrx.com/relenza/price#/?distance=19&filter-location=&coords=&label=Relenza&form=inhaler&strength=5mg&quantity=custom&qty-custom=1845&language=&store-chain=>.

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
				inhalers ¹²⁵ <ul style="list-style-type: none"> Price quote for 11,339 ten-day regimens of inhalers¹²⁶ 	
Mono-Therapy: Antiviral/Amantadine (adamantane drug)	↓ Virus Rep: Yes ↓ Imm. Resp: No Other: N/A	1,845 = \$3,250. 5,667 = \$9,960. 11,339 = \$19,900.	Bulk Store: Yes Cold Chain: No	GoodRx.com used, generic selected, capsules of 100mg each, one cap. per day for ten days <ul style="list-style-type: none"> Price quote for 1,845 ten-day regimens¹²⁷ Price quote for 5,667 ten-day regimens¹²⁸ Price quote for 11,339 ten-day regimens¹²⁹ 	No

¹²⁵ GoodRx.com, “Relenza,” (n.d.), <http://www.goodrx.com/relenza/price#/?distance=19&filter-location=&coords=&label=Relenza&form=inhaler&strength=5mg&quantity=custom&qty-custom=5667&language=&store-chain=>.

¹²⁶ GoodRx.com, “Relenza,” (n.d.), <http://www.goodrx.com/relenza/price#/?distance=19&filter-location=&coords=&label=Relenza&form=inhaler&strength=5mg&quantity=custom&qty-custom=11339&language=&store-chain=>.

¹²⁷ GoodRx.com, “Amantadine,” (n.d.), <http://www.goodrx.com/amantadine/price#/?distance=13&filter-location=&coords=&label=amantadine&form=capsule&strength=100mg&quantity=custom&qty-custom=1845&language=&store-chain=>.

¹²⁸ GoodRx.com, “Amantadine,” (n.d.), <http://www.goodrx.com/amantadine/price#/?distance=13&filter-location=&coords=&label=amantadine&form=capsule&strength=100mg&quantity=custom&qty-custom=5667&language=&store-chain=>.

¹²⁹ GoodRx.com, “Amantadine,” (n.d.), <http://www.goodrx.com/amantadine/price#/?distance=13&filter-location=&coords=&label=amantadine&form=capsule&strength=100mg&quantity=custom&qty-custom=11339&language=&store-chain=>.

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
Mono-Therapy: Antiviral/Rimantadine (adamantane drug)	↓ Virus Rep: Yes ↓ Imm. Resp: No Other: N/A	1,845 = \$52K 5,667 = \$161K 11,339 = \$321K	Bulk Store: Yes Cold Chain: No	GoodRx.com used, generic selected, tablets of 100mg each, one tablet per day for ten days <ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens¹³⁰ • Price quote for 5,667 ten-day regimens¹³¹ • Price quote for 11,339 ten-day regimens¹³² 	No
Mono-Therapy: Antiviral/Ribavirin (nucleoside antimetabolite drug)	↓ Virus Rep: Yes ↓ Imm. Resp: No Other: N/A	1,845= \$23K 5,667= \$71K 11,339= \$142K	Bulk Store: Yes Cold Chain: No	GoodRx.com used, generic selected, capsules of 200mg each, one cap. per day for ten days <ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens¹³³ • Price quote for 5,667 ten-day regimens¹³⁴ 	Yes

¹³⁰ GoodRx.com, “Rimantadine,” (n.d.), <http://www.goodrx.com/rimantadine/price#/?distance=13&filter-location=&coords=&label=rimantadine&form=tablet&strength=100mg&quantity=custom&qty-custom=18450&language=&store-chain=>.

¹³¹ GoodRx.com, “Rimantadine,” (n.d.), <http://www.goodrx.com/rimantadine/price#/?distance=13&filter-location=&coords=&label=rimantadine&form=tablet&strength=100mg&quantity=custom&qty-custom=56670&language=&store-chain=>.

¹³² GoodRx.com, “Rimantadine,” (n.d.), <http://www.goodrx.com/rimantadine/price#/?distance=13&filter-location=&coords=&label=rimantadine&form=tablet&strength=100mg&quantity=custom&qty-custom=113390&language=&store-chain=>.

¹³³ GoodRx.com, “Ribavirin,” (n.d.), <http://www.goodrx.com/ribavirin/price#/?distance=13&filter-location=&coords=&label=ribavirin&form=capsule&strength=200mg&quantity=custom&qty-custom=18450&language=&store-chain=>.

¹³⁴ GoodRx.com, “Ribavirin,” (n.d.), <http://www.goodrx.com/ribavirin/price#/?distance=13&filter-location=&coords=&label=ribavirin&form=capsule&strength=200mg&quantity=custom&qty-custom=56670&language=&store-chain=>.

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
				Price quote for 11,339 ten-day regimens ¹³⁵	
Mono-Therapy: Antibiotics <u>Fluoroquinolone Class:</u> Ciprofloxacin	↓ Virus Rep: No ↓ Imm. Resp: No Other: Can treat secondary bacterial infections	1,845= \$5K 5,667= \$14K 11,339= \$28K	Bulk Store: Yes Cold Chain: No	GoodRx.com used, generic selected, tablet of 500mg each, one tablet per day for ten days <ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens¹³⁶ • Price quote for 5,667 ten-day regimens¹³⁷ • Price quote for 11,339 ten-day regimens¹³⁸ 	No
Mono-Therapy: Antibiotics <u>Tetracycline Class:</u> Doxycycline hyclate	↓ Virus Rep: No ↓ Imm. Resp: No Other: Can treat secondary bacterial infections	1,845= \$89K 5,667= \$273K 11,339= \$546K	Bulk Store: Yes Cold Chain: No	GoodRx.com used, generic selected, capsule of 100mg each, one cap. per day for ten days <ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens¹³⁹ 	No

¹³⁵ GoodRx.com, “Ribavirin,” (n.d.), <http://www.goodrx.com/ribavirin/price#/?distance=13&filter-location=&coords=&label=ribavirin&form=capsule&strength=200mg&quantity=custom&qty-custom=113390&language=&store-chain=>.

¹³⁶ GoodRx.com, “Cipro,” (n.d.), <http://www.goodrx.com/cipro/price#/?distance=13&filter-location=&coords=&label=ciprofloxacin&form=tablet&strength=500mg&quantity=custom&qty-custom=18450&language=&store-chain=>.

¹³⁷ GoodRx.com, “Cipro,” (n.d.), <http://www.goodrx.com/cipro/price#/?distance=13&filter-location=&coords=&label=ciprofloxacin&form=tablet&strength=500mg&quantity=custom&qty-custom=56670&language=&store-chain=>.

¹³⁸ GoodRx.com, “Cipro,” (n.d.), <http://www.goodrx.com/cipro/price#/?distance=13&filter-location=&coords=&label=ciprofloxacin&form=tablet&strength=500mg&quantity=custom&qty-custom=113390&language=&store-chain=>.

¹³⁹ GoodRx.com, “Doxycycline Hyclate,” (n.d.), <http://www.goodrx.com/doxycycline-hyclate/price#/?distance=13&filter-location=&coords=&label=doxycycline+hyclate&form=capsule&strength=100mg&quantity=custom&qty-custom=18450&language=&store-chain=>.

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
				<ul style="list-style-type: none"> Price quote for 5,667 ten-day regimens¹⁴⁰ Price quote for 11,339 ten-day regimens¹⁴¹ 	
Mono-Therapy: Antibiotics <u>Penicillin Class:</u> Amoxicillin	↓ Virus Rep: No ↓ Imm. Resp: No Other: Can treat secondary bacterial infections	1,845= \$2K 5,667= \$6.2K 11,339= \$12.3K	Bulk Store: Yes Cold Chain: No	GoodRx.com used, generic selected, capsule of 500mg each, one cap. per day for ten days <ul style="list-style-type: none"> Price quote for 1,845 ten-day regimens¹⁴² Price quote for 5,667 ten-day regimens¹⁴³ Price quote for 11,339 ten-day regimens¹⁴⁴ 	No

¹⁴⁰ GoodRx.com, “Doxycycline Hyclate,” (n.d.), <http://www.goodrx.com/doxycycline-hyclate/price#/?distance=13&filter-location=&coords=&label=doxycycline+hyclate&form=capsule&strength=100mg&quantity=custom&qty-custom=56670&language=&store-chain=>.

¹⁴¹ GoodRx.com, “Doxycycline Hyclate,” (n.d.), <http://www.goodrx.com/doxycycline-hyclate/price#/?distance=13&filter-location=&coords=&label=doxycycline+hyclate&form=capsule&strength=100mg&quantity=custom&qty-custom=113390&language=&store-chain=>.

¹⁴² GoodRx.com, “Amoxicillin,” (n.d.), <http://www.goodrx.com/amoxicillin/price#/?distance=13&filter-location=&coords=&label=amoxicillin&form=capsule&strength=500mg&quantity=custom&qty-custom=18450&language=&store-chain=>.

¹⁴³ GoodRx.com, “Amoxicillin,” (n.d.), <http://www.goodrx.com/amoxicillin/price#/?distance=13&filter-location=&coords=&label=amoxicillin&form=capsule&strength=500mg&quantity=custom&qty-custom=56670&language=&store-chain=>.

¹⁴⁴ GoodRx.com, “Amoxicillin,” (n.d.), <http://www.goodrx.com/amoxicillin/price#/?distance=13&filter-location=&coords=&label=amoxicillin&form=capsule&strength=500mg&quantity=custom&qty-custom=113390&language=&store-chain=>.

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
Mono-Therapy: Statins Atorvastatin (Lipitor)	↓ Virus Rep: No ↓ Imm. Resp: Yes Other: N/A	1,845 = \$8.8K 5,667 = \$27K 11,339 = \$55K	Bulk Store: Yes Cold Chain: No	GoodRx.com used, generic selected, tablet of 40mg each, one tablet per day for ten days <ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens¹⁴⁵ • Price quote for 5,667 ten-day regimens¹⁴⁶ • Price quote for 11,339 ten-day regimens¹⁴⁷ 	Yes
Mono-Therapy: Statins Rosuvastatin (Crestor)	↓ Virus Rep: No ↓ Imm. Resp: Yes Other: N/A	1,845 = \$105K 5,667 = \$322K 11,339 = \$645K	Bulk Store: Yes Cold Chain: No	GoodRx.com used, brand name only avail., tablet of 40mg each, one tablet per day for ten days <ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens¹⁴⁸ • Price quote for 5,667 ten-day regimens¹⁴⁹ 	No

¹⁴⁵ GoodRx.com, “Lipitor,” (n.d.), <http://www.goodrx.com/lipitor/price#/?distance=13&filter-location=&coords=&label=atorvastatin&form=tablet&strength=40mg&quantity=custom&qty-custom=18450&language=&store-chain=>.

¹⁴⁶ GoodRx.com, “Lipitor,” (n.d.), <http://www.goodrx.com/lipitor/price#/?distance=13&filter-location=&coords=&label=atorvastatin&form=tablet&strength=40mg&quantity=custom&qty-custom=56670&language=&store-chain=>.

¹⁴⁷ GoodRx.com, “Lipitor,” (n.d.), <http://www.goodrx.com/lipitor/price#/?distance=13&filter-location=&coords=&label=atorvastatin&form=tablet&strength=40mg&quantity=custom&qty-custom=113390&language=&store-chain=>.

¹⁴⁸ GoodRx.com, “Crestor,” (n.d.), <http://www.goodrx.com/crestor/price#/?distance=13&filter-location=&coords=&label=Crestor&form=tablet&strength=40mg&quantity=custom&qty-custom=18450&language=&store-chain=>.

¹⁴⁹ GoodRx.com, “Crestor,” (n.d.), <http://www.goodrx.com/crestor/price#/?distance=13&filter-location=&coords=&label=Crestor&form=tablet&strength=40mg&quantity=custom&qty-custom=56670&language=&store-chain=>.

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
				<ul style="list-style-type: none"> Price quote for 11,339 ten-day regimens¹⁵⁰ 	
Mono-Therapy: Statins Simvastatin (Zocor)	↓ Virus Rep: No ↓ Imm. Resp: Yes Other: N/A	1,845 = \$2K 5,667 = \$6K 11,339 = \$12K	Bulk Store: Yes Cold Chain: No	GoodRx.com used, generic selected, tablet of 40mg each, one tablet per day for ten days <ul style="list-style-type: none"> Price quote for 1,845 ten-day regimens¹⁵¹ Price quote for 5,667 ten-day regimens¹⁵² Price quote for 11,339 ten-day regimens¹⁵³ 	Yes
Mono-Therapy: Statins Gemfibrozil (Lopid)	↓ Virus Rep: No ↓ Imm. Resp: Yes Other: N/A	1,845 = \$4K 5,667 = \$12.4K 11,339 = \$25K	Bulk Store: Yes Cold Chain: No	GoodRx.com used, generic selected, tablet of 600mg each, one tablet per day for ten days	Yes

¹⁵⁰ GoodRx.com, “Crestor” n.d., <http://www.goodrx.com/crestor/price#/?distance=13&filter-location=&coords=&label=Crestor&form=tablet&strength=40mg&quantity=custom&qty-custom=113390&language=&store-chain=>.

¹⁵¹ GoodRx.com, “Zocor,” (n.d.), <http://www.goodrx.com/zocor/price#/?distance=13&filter-location=&coords=&label=simvastatin&form=tablet&strength=40mg&quantity=custom&qty-custom=18450&language=&store-chain=>.

¹⁵² GoodRx.com, “Zocor,” (n.d.), <http://www.goodrx.com/zocor/price#/?distance=13&filter-location=&coords=&label=simvastatin&form=tablet&strength=40mg&quantity=custom&qty-custom=56670&language=&store-chain=>.

¹⁵³ GoodRx.com, “Zocor,” (n.d.), <http://www.goodrx.com/zocor/price#/?distance=13&filter-location=&coords=&label=simvastatin&form=tablet&strength=40mg&quantity=custom&qty-custom=113390&language=&store-chain=>.

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
				<ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens¹⁵⁴ • Price quote for 5,667 ten-day regimens¹⁵⁵ • Price quote for 11,339 ten-day regimens¹⁵⁶ 	
Mono-Therapy: Interferon- α 2b Intron-A	↓ Virus Rep: No ↓ Imm. Resp: Yes Other: N/A	1,845= \$3.7M 5,667= \$11.4M 11,339= \$23M	Bulk Store: Yes Cold Chain: No	GoodRx.com used, brand name only avail., vial of 1ml of 10miu, one vial per day for ten days <ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens¹⁵⁷ • Price quote for 5,667 ten-day regimens¹⁵⁸ • Price quote for 	No

¹⁵⁴ GoodRx.com, “Lopid,” (n.d.), <http://www.goodrx.com/lopid/price#/?distance=13&filter-location=&coords=&label=gemfibrozil&form=tablet&strength=600mg&quantity=custom&qty-custom=18450&language=&store-chain=>.

¹⁵⁵ GoodRx.com, “Lopid,” (n.d.), <http://www.goodrx.com/lopid/price#/?distance=13&filter-location=&coords=&label=gemfibrozil&form=tablet&strength=600mg&quantity=custom&qty-custom=56670&language=&store-chain=>.

¹⁵⁶ GoodRx.com, “Lopid,” (n.d.), <http://www.goodrx.com/lopid/price#/?distance=13&filter-location=&coords=&label=gemfibrozil&form=tablet&strength=600mg&quantity=custom&qty-custom=113390&language=&store-chain=>.

¹⁵⁷ GoodRx.com, “Intron A,” (n.d.), <http://www.goodrx.com/intron-a/price#/?distance=19&filter-location=&coords=&label=Intron+A&form=vial&strength=1ml+of+10miu&quantity=custom&qty-custom=18450&language=&store-chain=>.

¹⁵⁸ GoodRx.com, “Intron A,” (n.d.), <http://www.goodrx.com/intron-a/price#/?distance=19&filter-location=&coords=&label=Intron+A&form=vial&strength=1ml+of+10miu&quantity=custom&qty-custom=56670&language=&store-chain=>.

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
				11,339 ten-day regimens ¹⁵⁹	
Mono-Therapy: Interferon-α2b PegIntron	↓ Virus Rep: No ↓ Imm. Resp: Yes Other: N/A	1,845= \$14.8M 5,667= \$45.6M 11,339= \$91.3M	Bulk Store: No Cold Chain: Yes	GoodRx.com used, brand name only avail., vials of 150mcg/0.5ml, one vial per day for ten days <ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens¹⁶⁰ • Price quote for 5,667 ten-day regimens¹⁶¹ • Price quote for 11,339 ten-day regimens¹⁶² 	No
Mono-Therapy: Interferon-β1a Avonex	↓ Virus Rep: No ↓ Imm. Resp: Yes Other: N/A	1,845= \$21M 5,667= \$65M 11,339= \$130M	Bulk Store: No Cold Chain: Yes	GoodRx.com used, brand name only avail., vial of 30mcg/0.5ml, one vial per day for ten days <ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens¹⁶³ 	No

¹⁵⁹ GoodRx.com, “Intron A,” (n.d.), <http://www.goodrx.com/intron-a/price#/?distance=19&filter-location=&coords=&label=Intron+A&form=vial&strength=1ml+of+10miu&quantity=custom&qty-custom=113390&language=&store-chain=>.

¹⁶⁰ GoodRx.com, “Pegintron,” (n.d.), <http://www.goodrx.com/pegintron/price#/?distance=19&filter-location=&coords=&label=Pegintron&form=vial&strength=150mcg%2F0.5ml&quantity=custom&qty-custom=18450&language=&store-chain=>.

¹⁶¹ GoodRx.com, “Pegintron,” (n.d.), <http://www.goodrx.com/pegintron/price#/?distance=19&filter-location=&coords=&label=Pegintron&form=vial&strength=150mcg%2F0.5ml&quantity=custom&qty-custom=56670&language=&store-chain=>.

¹⁶² GoodRx.com, “Pegintron,” (n.d.), <http://www.goodrx.com/pegintron/price#/?distance=19&filter-location=&coords=&label=Pegintron&form=vial&strength=150mcg%2F0.5ml&quantity=custom&qty-custom=113390&language=&store-chain=>.

¹⁶³ GoodRx.com, “Avonex,” (n.d.), <http://www.goodrx.com/avonex/price#/?distance=19&filter-location=&coords=&label=Avonex&form=dose+pack&strength=vial+of+30mcg%2F0.5ml&quantity=custom&qty-custom=18450&language=&store-chain=>.

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
				<ul style="list-style-type: none"> Price quote for 5,667 ten-day regimens¹⁶⁴ Price quote for 11,339 ten-day regimens¹⁶⁵ 	
Mono-Therapy: Interferon-β1a Rebif	↓ Virus Rep: No ↓ Imm. Resp: Yes Other: N/A	1,845= \$9M 5,667= \$28M 11,339= \$56M	Bulk Store: No Cold Chain: Yes	GoodRx.com used, brand name only avail., carton of 12 syringes, each syringe is 44mcg, one syringe per day for ten days <ul style="list-style-type: none"> Price quote for 1,845 ten-day regimens¹⁶⁶ Price quote for 5,667 ten-day regimens¹⁶⁷ Price quote for 11,339 ten-day regimens¹⁶⁸ 	No
Mono-Therapy: Corticosteroids	↓ Virus Rep: No ↓ Imm. Resp: Yes Other: Anti-	1,845= \$29K 5,667= \$89K 11,339= \$178K	Bulk Store: Yes Cold Chain: No	GoodRx.com used, generic selected, dose packs of tablets in	No

¹⁶⁴ GoodRx.com, “Avonex,” (n.d.), <http://www.goodrx.com/avonex/price#/?distance=19&filter-location=&coords=&label=Avonex&form=dose+pack&strength=vial+of+30mcg%2F0.5ml&quantity=custom&qty-custom=56670&language=&store-chain=>.

¹⁶⁵ GoodRx.com, “Avonex,” (n.d.), <http://www.goodrx.com/avonex/price#/?distance=19&filter-location=&coords=&label=Avonex&form=dose+pack&strength=vial+of+30mcg%2F0.5ml&quantity=custom&qty-custom=113390&language=&store-chain=>.

¹⁶⁶ GoodRx.com, “Rebif,” (n.d.), <http://www.goodrx.com/rebif/price#/?distance=19&filter-location=&coords=&label=Rebif&form=carton&strength=12+syringes+of+44mcg&quantity=custom&qty-custom=1845&language=&store-chain=>.

¹⁶⁷ GoodRx.com, “Rebif,” (n.d.), <http://www.goodrx.com/rebif/price#/?distance=19&filter-location=&coords=&label=Rebif&form=carton&strength=12+syringes+of+44mcg&quantity=custom&qty-custom=5667&language=&store-chain=>.

¹⁶⁸ GoodRx.com, “Rebif,” (n.d.), <http://www.goodrx.com/rebif/price#/?distance=19&filter-location=&coords=&label=Rebif&form=carton&strength=12+syringes+of+44mcg&quantity=custom&qty-custom=11339&language=&store-chain=>.

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
Prednisone	inflammatory			10mg w/ 21 tablets per pack, two tablets per day for ten days <ul style="list-style-type: none"> • Price quote for 1,845 ten-day regimens¹⁶⁹ • Price quote for 5,667 ten-day regimens¹⁷⁰ • Price quote for 11,339 ten-day regimens¹⁷¹ 	
Mono-Therapy: Herbal medicines	↓ Virus Rep: No ↓ Imm. Resp: Yes Other: N/A	1,845= N/A 5,667= N/A 11,339= N/A	Bulk Store: Yes Cold Chain: No	<u>None</u> are FDA licensed for Treatment of novel/pandemic strain viruses	No
Combo-Therapy: Oseltamivir + Rlenza	↓ Virus Rep: Yes ↓ Imm. Resp: No Other: N/A	1,845 = \$320K 5,667= \$984K 11,339= \$1.25M	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Oseltamivir + Ribavirin	↓ Virus Rep: Yes ↓ Imm. Resp: No Other: N/A	1,845 = \$225K 5,667= \$691K 11,339= \$1.38M	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Rlenza + Ribavirin	↓ Virus Rep: Yes ↓ Imm. Resp: No Other: N/A	1,845 = \$141K 5,667= \$435K 11,339= \$870K	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No

¹⁶⁹ GoodRx.com, "Prednisone," (n.d.), <http://www.goodrx.com/prednisone/price#/?distance=19&filter-location=&coords=&label=prednisone&form=dose+pack&strength=21+tablets+of+10mg&quantity=custom&qty-custom=1845&language=&store-chain=>.

¹⁷⁰ GoodRx.com, "Prednisone," (n.d.), <http://www.goodrx.com/prednisone/price#/?distance=19&filter-location=&coords=&label=prednisone&form=dose+pack&strength=21+tablets+of+10mg&quantity=custom&qty-custom=5667&language=&store-chain=>.

¹⁷¹ GoodRx.com, "Prednisone," (n.d.), <http://www.goodrx.com/prednisone/price#/?distance=19&filter-location=&coords=&label=prednisone&form=dose+pack&strength=21+tablets+of+10mg&quantity=custom&qty-custom=11339&language=&store-chain=>.

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
Combo-Therapy: Amantadine + Ribavirin	↓ Virus Rep: Yes ↓ Imm. Resp: No Other: N/A	1,845 = \$26,250. 5,667= \$80,960. 11,339= \$162K	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Antivirals + Statins Oseltamivir + Atorvastatin (Lipitor)	↓ Virus Rep: Yes ↓ Imm. Resp: Yes Other: N/A	1,845 = \$211K 5,667= \$647K 11,339= \$1.29M	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Antivirals + Statins Oseltamivir + Rosuvastatin (Crestor)	↓ Virus Rep: Yes ↓ Imm. Resp: Yes Other: N/A	1,845 = \$307K 5,667= \$942K 11,339= \$1.9M	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Antivirals + Statins Oseltamivir + Simvastatin (Zocor)	↓ Virus Rep: Yes ↓ Imm. Resp: Yes Other: N/A	1,845 = \$204K 5,667= \$626K 11,339= \$1.25M	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Antivirals + Statins Oseltamivir + Gemfibrozil (Lopid)	↓ Virus Rep: Yes ↓ Imm. Resp: Yes Other: N/A	1,845 = \$206K 5,667= \$632K 11,339= \$1.26M	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Antivirals + Statins Relenza + Atorvastatin (Lipitor)	↓ Virus Rep: Yes ↓ Imm. Resp: Yes Other: N/A	1,845 = \$127K 5,667= \$145K 11,339= \$783K	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Antivirals + Statins Relenza + Rosuvastatin (Crestor)	↓ Virus Rep: Yes ↓ Imm. Resp: Yes Other: N/A	1,845 = \$223K 5,667= \$686K 11,339= \$1.4M	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Antivirals + Statins Relenza + Simvastatin (Zocor)	↓ Virus Rep: Yes ↓ Imm. Resp: Yes Other: N/A	1,845 = \$120K 5,667= \$370K 11,339= \$740K	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy:	↓ Virus Rep: Yes	1,845 = \$122K	Bulk Store: Yes	Combo packs not avail.,	No

Therapy	Medical Efficacy	Cost	Logistical Considerations	Citations	Good Choice for a State Stockpile? Yes or No
Antivirals + Statins Relenza + Gemfibrozil (Lopid)	↓ Imm. Resp: Yes Other: N/A	5,667= \$377K 11,339= \$753K	Cold Chain: No	combine previously cited mono-therapy's prices.	
Combo-Therapy: Antivirals + Statins Ribavirin + Atorvastatin (Lipitor)	↓ Virus Rep: Yes ↓ Imm. Resp: Yes Other: N/A	1,845 = \$32K 5,667= \$98K 11,339= \$197K	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Antivirals + Statins Ribavirin + Rosuvastatin (Crestor)	Virus Rep: Yes ↓ Imm. Resp: Yes Other: N/A	1,845 = \$128K 5,667= \$393K 11,339= \$787K	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Antivirals + Statins Ribavirin + Simvastatin (Zocor)	Virus Rep: Yes ↓ Imm. Resp: Yes Other: N/A	1,845 = \$25K 5,667= \$77K 11,339= \$154K	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Antivirals + Statins Ribavirin + Gemfibrozil (Lopid)	↓ Virus Rep: Yes ↓ Imm. Resp: Yes Other: N/A	1,845 = \$27K 5,667= \$84K 11,339= \$167K	Bulk Store: Yes Cold Chain: No	Combo packs not avail., combine previously cited mono-therapy's prices.	No
Combo-Therapy: Interferon-α2b + Ribavirin, PegIntron/Rebetol Combo Pack	↓ Virus Rep: Yes ↓ Imm. Resp: Yes Other: N/A	1,845 = \$0 5,667= \$0 11,339= \$0	Bulk Store: No Cold Chain: Yes	No Data Available	No Data Available

V. DISCUSSION

The idea behind this thesis was born when the Nevada PHP program logistician and the author were tasked with conducting an inventory of the state's stockpile of antivirals and PPE in the Spring of 2013. At that time, the CDC was convening weekly teleconferences with all of its state-level partners to discuss the increasing H7N9 threat. As the weekly teleconferences took on a more somber tone, those who serve within the state of Nevada's PHP program began a pre-incident command structure to assist in the state's preparations and planning. One of the first orders of business by that command group was to inventory and update the state response plans for pandemics, as well as to verify the amount of all the antivirals and PPE contained within the state PHP program's warehouse. It was in the midst of these efforts at the state PHP program's warehouse when the logistician and the author began discussing their concerns about "what to do if some or all these antivirals are not effective" and "what other tools in the public health 'toolbox' are available in response to a pandemic?" This thesis is the author's attempt to answer those two questions and to help make Nevada better prepared to respond to such a daunting task as facing a pandemic strain virus (be that a type-A influenza virus or a HCoV).

One of the more apparent issues revealed by the analysis to this research is how expensive a potential state-level stockpile could become, particularly when brand name medications are considered as candidates. Although medical efficacy does not appear to be as significant a limiting factor, cost and logistical considerations certainly narrow the field down to only a few options. In this era of declining grant funds, and an all-hazards approach, could (and some would even argue should) these "few options" even be considered as a possible investment in state-level prevention efforts?

A. THE PARADOX OF PREVENTION

Dr. Harvey V. Fineberg recently discussed the paradox of prevention issue in an article he wrote for the *Journal of the American Medical Association (JAMA)*. Dr. Fineberg's article provides a list of a dozen reasons as to why "prevention is so regularly

resisted;” he then continues to explain how preventative approaches differ from the more easily accepted curative approaches within American culture.¹⁷² For a graduate thesis interested in exploring the idea of expanding a state’s existing stockpile of curative approaches to include more treatment options, the Fineberg article helps describe the cultural and political environment in which that proposal would unfold. This reality may help to formulate a series of options for public health leadership to decide upon. An example of providing “options” to public health leadership (at the state level) could be, 1) select a therapy or therapies, and purchase the full range of regimens in one large expenditure of funds, 2) select a therapy or therapies to purchase over multiple budget periods (a.k.a. incremental approach), 3) select a therapy or therapies and not purchase them, but instead establish contracts with pharmaceutical vendors to purchase them based off a pre-designated trigger (e.g., pandemic of sustained human-to-human transmission declared by the CDC and/or WHO, etc.) in times of need, or 4) not select any new therapy or therapies, and continue to rely on existing state stockpiles and projected SNS materials.

B. KEY CONCEPTS

1. Stockpile Cost As a Percentage of a State’s Public Health Preparedness Budget

Within the previous chapter, four therapies were identified as being a “good choice for a state stockpile:” a generic antiviral called Ribavirin, and three statins called generic Lipitor, generic Zocor, and generic Gemfibrozil. For each of those therapies, how do their price quotes compare to the current fiscal year’s total PHP grant for Nevada? To answer that question, it will be necessary to know what amounts of grant funding states (such as Nevada) are awarded. For many awardees, to include Nevada, their state and local PHP programs are completely funded by an aligned federal grant formed by the Hospital Preparedness Program (HPP) and the Public Health Emergency Preparedness (PHEP) cooperative agreement. For each year of that aligned grant, the CDC publishes

¹⁷² Harvey V. Fineberg, “The Paradox of Disease Prevention: Celebrated in Principle, Resisted in Practice,” *Journal of the American Medical Association [JAMA]* 310, no. 1 (2013): 85–90.

the amount of funding awarded to each state and territory on its website.¹⁷³ The CDC's annual award is based off a funding formula that "includes a base amount for each awardee plus population-based funding."¹⁷⁴ According to the CDC's publication for the current budget period (a.k.a. Fiscal Year 2013), the state of Nevada receives the following amounts of federal HPP/PHEP grant funding.

- HPP Budget Period 2 (Fiscal Year 2013) Funding: \$3,256,408.00¹⁷⁵
- PHEP Budget Period 2 (Fiscal Year 2013) Funding: \$6,482,206.00¹⁷⁶
- Total Funding (HPP + PHEP) for Budget Period 2: \$9,738,614.00

When the price quotes for each of the therapies listed in the previous chapter are taken, and divided into Nevada's total PHP funding for the current budget period (e.g., \$9.7M), those calculations result in the following options.

a. Option 1—Generic Ribavirin

1,845 ten-day regimens = \$23,000, which would be approximately 0.23% of the PHP budget
5,667 ten-day regimens = \$71,000, which would be approximately 0.73% of the PHP budget
11,339 ten-day regimens = \$142,000, which would be approximately 1.5% of the PHP budget

b. Option 2—Generic Lipitor

1,845 ten-day regimens = \$8,800, which would be approximately 0.09% of the PHP budget
5,667 ten-day regimens = \$27,000, which would be approximately 0.28% of the PHP budget
11,339 ten-day regimens = \$55,000, which would be approximately 0.6% of the PHP budget

¹⁷³ Centers for Disease Control and Prevention [CDC], *Procurement and Grants Office, Instructions for Preparing an Interim Progress Report, Catalog of Federal Domestic Assistance (CFDA) Number: 93.074—National Bioterrorism Hospital Preparedness Program and Public Health Emergency Preparedness Program Funding Opportunity Announcement (FOA) Number: CDC-RFA-TP12-120102CONT13*, http://www.cdc.gov/phpr/documents/TP12-120102CONT13_AMENDMENT_03_25_13.pdf.

¹⁷⁴ *Ibid.*, 27.

¹⁷⁵ *Ibid.*, Appendix 1, 31.

¹⁷⁶ *Ibid.*, Appendix 2, 33.

c. Option 3—Generic Zocor

1,845 ten-day regimens = \$2,000, which would be approximately 0.02% of the PHP budget

5,667 ten-day regimens = \$6,000, which would be approximately 0.06% of the PHP budget

11,339 ten-day regimens = \$12,000, which would be approximately 0.12% of the PHP budget

d. Option 4—Generic Gemfibrozil

1,845 ten-day regimens = \$4,000, which would be approximately 0.04% of the PHP budget

5,667 ten-day regimens = \$12,400, which would be approximately 0.13% of the PHP budget

11,339 ten-day regimens = \$25,000, which would be approximately 0.26% of the PHP budget

2. Balancing Therapies On-Hand with Those That Could be Needed

Quite a few therapies listed within this thesis appear to be good choices for a state stockpile as well; yet, they are not included amongst the four candidate therapies: why is this? For some of those therapies, they are already included within the CDC's SNS, and have been factored into state planning and projections for a response to a biological threat (e.g., antibiotics for use against bacterial threats, such as bacillus anthracis/anthrax, antivirals for use against pandemic strain influenza viruses, etc.). As discussed previously in this thesis, a portion of those SNS assets (e.g., antivirals and PPE) remain in state stockpiles as leftovers from the 2009–2010 H1N1 influenza response. In the case of Nevada, those materials account for quite a substantial state stockpile (these current totals for Nevada are as of June 2013).

- Oseltamivir/Tamiflu: 54,808 regimens of various dosages (e.g., 30mg, 45mg, 75mg, pediatric oral suspension, etc.)
- Zanamivir/Relenza: 15,680 regimens of 5mg inhalers

When those existing state stockpiles are compared against the hospitalization rate projections calculated previously (e.g., 1,845 / 5,667 / 11,339), they account for a sizeable portion of what Nevada would require to help treat or to provide prophylaxis to its citizens against a novel virus. When considering the fact that these existing stockpiles account for only 25% of each state's total allotment at the CDC, then the purchase of

additional regimens (at great cost) is a difficult argument to make to public health leadership trying to “do more with less” in their budgets.

When the issue of creating a state stockpile of antibiotics is raised, the same could be said for the antibiotics identified in the previous chapter, which are also included within the CDC’s SNS and would come in large numbers. An example would be the CDC’s 12-hour push package, which would arrive with 500,000 10-day regimens of various antibiotics (e.g., Ciprofloxacin, Doxycycline, etc.).¹⁷⁷ As plentiful as the 12-hour push package’s materials may be, that federal asset would be in high demand during a pandemic; thus, from a planning perspective, states may not be able to rely on that asset arriving to their jurisdiction during such a “high-demand” scenario. As impressive as the 12-hour push packages may be, they represent approximately 4% of the total assets controlled by the CDC’s DSNS. The remaining 96% of what the DSNS controls is called managed inventory (MI), and additional antibiotics are included within the MI as well. From a state-planning perspective, these materials within the MI are much more accessible in “high-demand” scenarios than those found within the 12-hour push package. When considering the fact that these existing federal stockpiles contain such large quantities of these therapies (in either the push package or the MI), then the purchase of additional regimens at a state-level is a difficult argument to make with public health leadership.

C. LESSONS LEARNED

Pandemics involving novel strain influenza viruses, or coronaviruses, appear to be emerging with greater frequency. Over the span of 15 years, public health has witnessed a series of pandemic viruses. In the late 1990s, the world watched the emergence of the H5N1 avian influenza virus (that continues to smolder in Asia); in 2003, the SARS coronavirus erupted out of southeast China; most recently, in 2009, the H1N1 influenza pandemic emanated out of Mexico. Currently, public health professionals are waiting and watching to see if H7N9 and MERS-CoV will become pandemic viruses. Just as

¹⁷⁷ Centers for Disease Control and Prevention [CDC], “Strategic National Stockpile (SNS),” (n.d.), <http://www.cdc.gov/phpr/stockpile/stockpile.htm>.

seismologists discuss when they believe “the big one” will occur in earthquake-prone places, such as San Francisco, public health professionals discuss when they believe the next “big one” (a.k.a. the next 1918-like pandemic) will occur. As the CDC and NIH are often quoted as saying, it is not “if” something like this will occur again but “when?”¹⁷⁸

1. Limitations to Interpretation

A few issues limited this research, most notably, the fact that it is attempting to plan for a virus that probably does not yet exist. Although the articles and books used in this research provide a glimpse into what the global public health community is discussing, they do not provide a definitive protocol on how to treat pandemic strain viruses. This research was also limited by a lack of knowing the full range of medical therapies available in the nation’s SNS. The agency responsible for screening, testing, and selecting medical countermeasures (MCM) for inclusion into the SNS is the Biomedical Advanced Research and Development Authority, more commonly referred to as BARDA.¹⁷⁹ For security reasons, the full list of what MCM are included within the nation’s stockpiles are not published openly; therefore, a comparison of the four therapies revealed through this research could not be made against a list of what BARDA has included in its stockpile roster.

In Chapter IV, the Nevada state demographer’s census data were used to help calculate the gross attack rate, the hospitalization rate, and the mortality rate estimates specific to Nevada in the aftermath of a pandemic. A key flaw to using this data is that it only reflects Nevada resident population, and does not compensate for the additional population of its visitors. Depending on the time of year, Nevada’s overall population can swell by nearly 20% with the addition of the state’s tourist population (e.g., New Years’ Eve celebrations on the Las Vegas Strip, etc.). As an example for two of the state’s largest cities, tourism data report that nearly 40 million visitors came to Las Vegas in

¹⁷⁸ Taubenberger and Morens, “1918 Influenza: The Mother of All Pandemics,” 20.

¹⁷⁹ Public Health Emergency [PHE], “BARDA Leadership Biographies,” (n.d.), <http://www.phe.gov/about/barda/bio/Pages/default.aspx>.

2012, and nearly 4.1 million visitors are expected to see Reno each year.¹⁸⁰ Estimates for tourist population are difficult to discern. Therefore, in an effort to keep the calculations as straight forward as possible, this research only calculated for Nevada residents as listed in the state's demography data.

Chapter IV also made heavy use of an online accessible (open source) pharmaceutical bulk price quoting website called GoodRx. As useful as this system was in providing citable price quotes, it would have been wise to run the same price quote calculations through a nationally published tool, such as Red Book. Based off consultations with colleagues who work in the pharmaceutical business, the Red Book price index would have been the most accurate with which to work. With access to the Red Book system being limited, its use would have hampered any citations linking price quotes used in this thesis to an accessible system.

2. Areas of Future Research

Since the emergence of H5N1 avian influenza in the late 1990s, the topic of expanding the roster of treatment and/or prophylaxis options in the face of a pandemic strain virus has received a great deal of discussion and study. With so many global/national/academic institutions within public health searching for new, and improving upon existing, drug therapies, the list of potential therapies will continue to expand. Future study will need to build upon this growing list of potential options. Those studies could look for effective options that not only address the virus replication and immune system challenges raised in this thesis, but they could possibly explore new pathways for limiting disease in people afflicted by pandemic strain viruses as well.

With the price of supplementing existing state stockpiles with more options, the issue of cost will undoubtedly continue. One of the first questions public health leaders are expected to ask would be if it is possible to receive this recommended therapy from the DSNS? To answer that question, it will be necessary to know if BARDA has included any or all of these recommended therapies into its national roster. In an effort to balance

¹⁸⁰ Las Vegas Convention and Visitors Authority, "Stats and Facts," (n.d.), <http://www.lvcva.com/stats-and-facts>; Reno/Tahoe Visitor, "General Information for 2012–2013," (n.d.), <http://www.renotahoevisitor.com/pdfs/VisitorMediaKit.pdf>, 1.

security concerns with research, perhaps future study could answer in a simple “yes” or “no” format if recommended therapies are included within the nation’s stockpile? For states that have conducted their own calculations to determine how many regimens they would need, then perhaps those estimates could be compared to the quantities included by BARDA in the stockpile as well?

If more time were available for this research, it would have been useful to quantify how large of a “logistical footprint” these proposed therapies would take in a state PHP program’s warehouse. Once a determination is made as to how many regimens of a therapy would be needed, the next logical step would be to convert those estimates into length/width/height calculations. Bulk items, such as medications and PPE, take up space within a warehouse, which is often described as volume (e.g., two square yards per pallet, etc.). Although the GoodRx website is useful in estimating how much a specific therapy would possibly cost, it does not provide any detail as to how much space those materials would need to occupy. The ability to convert bulk orders into detailed estimates for how much volume those materials would occupy in a warehouse is yet another useful piece of information for future studies to explore.

The next logistical consideration that would need to be included in a proposal to expand a state’s stockpile is the manufacturers’ recommended expiration date for each therapy. The shelf life of a stockpiled therapy would need to be as long as possible; thus, extending the benefit of investing in such a prevention strategy. An unintended benefit for Nevada when it received 25% of its allotted antivirals and PPE during the 2009/2010 H1N1 response is that the state had to develop strong systems to track/manage/destroy those materials as they expired. If future studies could build upon those newly acquired skill sets, and help improve the system that allow states to track and manage an expanded state stockpile, then that would also be useful for pandemic planning purposes.

D. RECOMMENDATIONS

In this environment of “do more with less,” it is difficult to provide a single recommendation that will bolster state response capabilities. In an effort to provide public health leaders with a set of options to choose from, this thesis lists four possible therapies

being recommended to state lawmakers from which to select. Although each of the options requires the addition of more medications to the state's existing stockpile, the options vary by when those materials are to be purchased.

Recommendation 1: Purchase Generic Lipitor, Generic Zocor and Generic Gemfibrozil to Supplement State Stockpiles in One Purchase

This recommendation would expand the current state stockpile to include three generic statins (Lipitor, Zocor and Gemfibrozil) that can help limit the body's immune response within patients suffering from pandemic viruses. This observed medical efficacy (of reducing a physiological response to infection, in this example, the cytokine storm) is particularly appealing because it is independent of a specific virus strain. Regardless of the viral strain infecting a patient and causing pneumonia, these statins will help lower the immune response to that infection within the lungs. For many people who fall ill with a pandemic strain virus, this lowering of their body's immune response within their lungs may be the difference between succumbing to the infection versus surviving the infection. From a medical efficacy point-of-view, they are appealing for the synergistic effect they have on pandemic strain viruses when used in tandem with antivirals (existing state stockpiles have two types of antivirals discussed previously). Although the scientific explanations behind these synergistic effects are still being studied, the literature makes a strong case for the use of antivirals and statins administered together as a complementary treatment option to healthcare providers. These recommended statins are appealing for other reasons as well. They are affordable at bulk rates, they are well known to both the public and healthcare providers, and they are easily stored long term in climate-controlled warehouses.

Three key limitations to this recommendation are: 1) statins do not have any efficacy when used as a prophylaxis against novel viruses; thus, they could only be used as a treatment therapy, 2) purchasing a stockpile all at once may lead to drug expiration dates that may be the same, or close together, and 3) the cost projections for the 11,339 tier will exceed the 1% limit set for Nevada's PHP budget (as discussed in Chapter III).

One of the many lessons that states learned from absorbing such a large inject of MCM in the aftermath of the 2009 H1N1 response was that many of those medications

would expire later en masse. Without fastidious attention to stockpile expiration dates, a state could lose a large portion of its stockpile quite literally overnight. Many of those planning considerations were learned through experience, and mitigated through budget planning and stockpile rotation. For this option to work, those same strategies would need to be employed.

Even for a worse-case planning scenario (e.g., the maximum lethality of a pandemic), the projected cost for purchasing all three statins would just barely fall within the 1% limit. The breakdowns of the projected percentage of Nevada's PHP budget are as follows in Table 7.

Table 7. Recommendation One Described as a Percentage of Nevada's PHP Budget

	1,845 ten-day regimens	5,667 ten-day regimens	11,339 ten-day regimens
Lipitor (generic)	0.09% of PHP Budget	0.28% of PHP Budget	0.6% of PHP Budget
Zocor (generic)	0.02% of PHP Budget	0.06% of PHP Budget	0.12% of PHP Budget
Gemfibrozil (generic)	0.04% of PHP Budget	0.13% of PHP Budget	0.26% of PHP Budget
Totals	0.15% of PHP Budget	0.47% of PHP Budget	0.98% of PHP Budget

For the price, and for the ease of storage, these three complementary therapies may help broaden the range of treatment options that Nevada's current state stockpile provides. From a state planning perspective, to have a set of affordable and complementary therapies that work independently of a specific virus strain would be a welcomed addition to a state-level stockpile.

Recommendation 2: Purchase Generic Ribavirin/Zocor/Gemfibrozil Incrementally over Multiple Budget Periods

As appealing as the first option may be, it may be a wise investment to expand the state's existing stockpile of antivirals to include another, Ribavirin, as well. The research

indicates that this additional antiviral therapy has significant medical efficacy when used either as a prophylaxis, or as a treatment. The research continues to discuss the synergistic effect this medication has when used in conjunction with other antivirals (e.g., Oseltamivir, Relenza, etc.), as well as statins. To have yet another prophylaxis and/or treatment option, that complements what is already on hand, would be a force multiplier within a public health response to a pandemic.

If the price to purchase any of these therapies in one large expenditure were too great, then perhaps a more incremental approach over a number of budget years would be more appealing? If the economic impact to the state's PHP budget could be spread over a few years, then the idea of adding Ribavirin to the list may be plausible as well. Although the generic version of this therapy at 11,339 ten-day regimens exceeds the 1% of total budget limit, that price may be easier to absorb if spread over many years. The breakdowns of the projected percentage of Nevada's PHP budget for Fiscal Year 2013 are as follows in Table 8.

Table 8. Recommendation Two Described as a Percentage of Nevada's PHP Budget

	1,845 ten-day regimens	5,667 ten-day regimens	11,339 ten-day regimens
Ribavirin (generic)	0.23% of PHP Budget	0.73% of PHP Budget	1.5% of PHP Budget
Zocor (generic)	0.02% of PHP Budget	0.06% of PHP Budget	0.12% of PHP Budget
Gemfibrozil (generic)	0.04% of PHP Budget	0.13% of PHP Budget	0.26% of PHP Budget
Totals	0.29% of PHP Budget	0.92% of PHP Budget	1.88% of PHP Budget

When each of these totals are divided by the 1% budget limit per fiscal year budget, the following estimates are generated for the number of years it would take to assemble each tier. For the 1,845 tier it would take one budget period; for the 5,667 tier, it too would take one budget period; and for the 11,339 tier, it would take approximately

two budget periods to assemble that amount of therapies. Each of these timeframes are strategic considerations for any state, with Nevada being no different. Therefore, committing to a long-term investment of this nature would require a great deal of support by public health leadership.

A benefit to compiling a state stockpile of this size, over these many years, is that stock rotation would be inherent in the system. As newer medications are brought into the stockpile, older medications would be rotated out as they expire. This cycle would help prevent that potential loss of a state stockpile “overnight” as was discussed previously.

Recommendation 3: Establish Purchasing Contracts for Generic Ribavirin/Zocor/Gemfibrozil in “Times of Need”

Stockpiles of any kind are by their very nature large investments in material, money, space, and staff hours. As budgets continue to decline, many leaders within government are hesitant to commit to this level of investment. However, federal preparedness grants are rather clear in determining what capabilities and resources state and local partners would need to “assure safer, more resilient, and better prepared communities.”¹⁸¹ Within the Public Health Emergency Preparedness Capabilities, the CDC and U.S. Department of Health and Human Services (DHHS) have defined what resource elements they consider key to accomplishing this resiliency and preparedness: “a public health agency has either the ability to have, or has access to, the resource element.”¹⁸² It is that second point about public health agencies having “access to” resource elements that would help support this recommendation.

Rather than purchase, maintain, and rotate supplemental therapies within an existing state stockpile, another option is for a state to create contracts with vendors that would be activated upon a pre-determined trigger. An example of such a trigger for pandemic influenza or coronavirus could be to prepare a pre-written state contract to

¹⁸¹ Centers for Disease Control and Prevention [CDC], Office of Public Health Preparedness and Response [PHPR], Public Health Preparedness Capabilities: National Standards for State and Local Planning, “Executive Summary,” March 2011, [http://www.cdc.gov/phpr/capabilities/executive summary.pdf](http://www.cdc.gov/phpr/capabilities/executive_summary.pdf), 2.

¹⁸² Ibid., 5.

purchase 1,845/5,667/11,339 ten-day regimens of therapy “A” (the exact wording could reflect any therapy) that would go into effect when the U.S. government declares Stage 4 (first confirmed human case in North America), or when the WHO declares Phase 6 (increased and sustained transmission in general population).¹⁸³ In this example, the action that made a contract go into effect was based off third party “triggers;” in reality, those could be pre-written to activate off a state health officer’s request, etc. This recommended option would provide a set of medical therapies known to have medical efficacy against pandemic viruses. Some of these therapies would provide additional prophylaxis and treatment options during a pandemic, while others could only be used for treatment. In each case, these medications would expand the current list of options available to public health and clinical providers during a pandemic.

From the perspective of logistics, this option would still require some planning considerations. Although the materials would be brought in during a “time of need,” they would still require enough space set aside somewhere for all these medications to be received and stored within a climate-controlled warehouse with little notice of their arrival. As was previously discussed, to plan properly for this scenario, a detailed estimate of their logistical footprint (a.k.a. how much space they would need to occupy within a warehouse) would need to be calculated as well. If such a contract would go in effect at some undetermined time, then the pre-planning for those materials would require that adequate square footage (defined in terms of length, width, and height) be ready to receive them.

E. SUMMARY

With the global population expected to increase by 50% in 50 years (from approximately six billion in the year 2000 to approximately nine billion by the year 2050), the world may be in an epoch of human history whereby pandemics involving

¹⁸³ World Health Organization [WHO], “Pandemic Influenza: WHO Global Pandemic Phases and Stages for Federal Government Response,” (n.d.). C:\Users\chdsstudent\AppData\Local\Microsoft\Windows\Temporary Internet Files\Content.IE5\S94DQWVQ\AppE.pdf, 56.

novel viruses may appear with greater frequency and lethality.¹⁸⁴ Existing plans and preparations at the federal, state and local level of government are comprised of a whole series of interventions, from mass vaccination and mass dispensing, to hygiene and social distancing. This research focused on one component of that broad set of interventions, treatment and prophylaxis.

Since the successful completion of the 2009–2010 response to the H1N1 pandemic, many states have acquired and maintained state stockpiles of antiviral medications and PPE. As those same states prepare for future pandemics involving novel viruses, some state planners are looking to expand their current stockpiles to include more treatment and prophylaxis options. This research identifies four such medications: an antiviral that could be used as a treatment option or as a prophylaxis option, called generic Ribavirin; three statins that could be employed solely as treatment options: generic Lipitor, generic Zocor, and generic Gemfibrozil.

With planning for pandemics that would involve viruses that may not yet exist, this ability to expand state stockpiles with more treatment and prophylaxis options may be a sound investment. Nearly all prevention efforts come with some kind of cost, be they in money, time, or space; yet, these recommended medical therapies are preventative efforts against some of the most dangerous threats posed to humanity, pandemics. This research is one state's attempt at exploring what other options may exist. This research has attempted to open a dialogue with other federal and state planners as they wrestle with the same challenges within their home agencies. As terrible as pandemics may be, sound precautions can be taken now to be better prepared for something (like a pandemic) tomorrow.

¹⁸⁴ World-o-meters, "World Population Clock," (n.d.), <http://www.worldometers.info/world-population/>.

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